PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

AOYAMA, Tamotsu
Aoyama & Partners
IMP Building
3-7, Shiromi 1-chome
Chuo-ku, Osaka-shi
Osaka 540
JAPON

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
05 November 1998 (05.11.98)

Applicant's or agent's file reference
660492

IMPORTANT NOTIFICATION

International application No.
PCT/JP97/03239

International filing date (day/month/year)
12 September 1997 (12.09.97)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
KOBAYASHI, Midori
647-2, Chougo
Fujisawa-shi
Kanagawa 252
Japan

State of Nationality: JP
State of Residence: JP
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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KOBAYASHI, Midori
Royal Court 306
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Yamato-shi
Kanagawa 242-0006
Japan

State of Nationality: JP
State of Residence: JP
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the [illegible] Office

[ ] [illegible]

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

[illegible]

M Sakai

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

AOYAMA, Tamotsu
Aoyama & Partners
IMP Building
3-7, Shiromi 1-chome
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JAPON

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)
24 June 1998 (24.06.98)

Applicant's or agent's file reference
660492

IMPORTANT NOTIFICATION

International application No.
PCT/JP97/03239

International filing date (day/month/year)
12 September 1997 (12.09.97)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

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State of Residence: JP
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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Japan

State of Nationality: JP
State of Residence: JP
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] ... [ ] ...

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer
M. Sakai

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 28 April 1998 (28.04.98)	
International application No. PCT/JP97/03239	**Applicant's or agent's file reference** 660492
International filing date (day/month/year) 12 September 1997 (12.09.97)	**Priority date** (day/month/year) 13 September 1996 (13.09.96)
Applicant KATO, Seishi et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   09 April 1998 (09.04.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer M. Sakai

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 660492	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/JP97/03239	International filing date *(day/month/year)* 12/09/1997	Priority date *(day/month/year)* 13/09/1996
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant SAGAMI CHEMICAL RESEARCH CENTER et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Name and mailing address of the IPEA

Fax (+49-89) 2399-4465

Authorized officer

Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP97/03239

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-116 as originally filed

Claims, No.:

1-4 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4 (partially).

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary

   ☒ the parts relating to claims Nos. 1-4 (partially).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP97/03239

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

see separate sheet

The following documents (D) are mentioned for the first time in this opinion/report; the numbering will be adhered to in the rest of the procedure:

D1...Gene, vol. 163, 1995, pages 193-196 (Yokoyama-Kobayashi et al.)
D2...Nuc. Acids Res., vol. 14, 1986, pages 4683-4690 (Von Heijne)
D3...Science, vol. 261, 1993, pages 600-603 (Tashiro et al.)

IV) Unity

1) The International Searching Authority made an objection concerning lack of unity within the application as originally filed (**Rule 13.1 - 13.3 PCT**).The objection is summarised below:

The following 9 inventions identified within originally filed **claims 1-4** are not so linked as to form a single general inventive concept:

Invention 1. DNAs relating to SEQ ID No 10 and 19 and protein relating to SEQ ID No 1 (**claims 1-4** partially).

Invention 2. DNAs relating to SEQ ID No 11 and 20 and protein relating to SEQ ID No 2 (**claims 1-4** partially).

Invention 3. DNAs relating to SEQ ID No 12 and 21 and protein relating to SEQ ID No 3 (**claims 1-4** partially).

Invention 4. DNAs relating to SEQ ID No 13 and 22 and protein relating to SEQ ID No 4 (**claims 1-4** partially).

Invention 5. DNAs relating to SEQ ID No 14 and 23 and protein relating to SEQ ID No 5 (**claims 1-4** partially).

[illegible] relating to SEQ ID

[illegible]

Invention 7. DNAs relating to SEQ ID No 16 and 25 and protein relating to SEQ ID

No 7 (**claims 1-4** partially).

Invention 8. DNAs relating to SEQ ID No 17 and 26 and protein relating to SEQ ID No 8 (**claims 1-4** partially).

Invention 9. DNAs relating to SEQ ID No 18 and 27 and protein relating to SEQ ID No 9 (**claims 1-4** partially).

3) The only common concept linking the above inventions is the presence of a secretory signal sequence. However, since secretory signal sequences and methods for detecting them were disclosed in the prior art (D1-D3), this concept is not novel.

4) In response to an invitation by the ISA, the applicant paid no additional search fees. Consequently, substantive examination has been carried out on invention 1, which has been searched and is considered to be the main invention, being that which is first mentioned in the claims.

V) Reasoned statement

Inventive Step

1) The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-4** does not involve an inventive step (**Rule 65.1 and 65.2 PCT**).

2) Although the application discloses nucleotide sequences corresponding to a cDNA clone isolated from a human cDNA library and the "best guess" open reading frame (ORF) identifiable with it, it provides no evidence of the in vitro translated polypeptide's biological role - the description only states on page 22 what it is not (i.e. RANTES). Consequently, the invention of the present application is merely

In this case any prior art compound, regardless of its technical properties, is

equally suitable as the starting point for making structural modifications and may be considered to represent "the closest prior art".

Starting from this point, the only technical problem which may be derived is how to provide a different compound.

Without the concomitant need to provide any particular technical effect, the skilled person would have the choice of an infinite number of equally obvious possible solutions. An arbitrary selection from this list cannot involve an inventive step because, in order to be patentable, a selection must be justified by a technical purpose, i.e. by a hitherto unknown or unexpected technical effect resulting from those structural features which distinguish the compound claimed from all the other possibilities.

Thus, for nucleotide and peptide sequences whose function is based purely upon surmise, inventive step cannot be acknowledged.

Furthermore, if an invention should provide a solution to a problem with reference to the background art (**Rule 5.1 (a) (iii) PCT**), the "invention" of the present application is insufficiently disclosed (**Article 5 PCT**) and unclear (**Article 6 PCT**), since it is left to the reader to perform the invention and determine what problem, if any, the isolated nucleotide or polypeptide sequences actually solve.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
660492		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 97/03239	12/09/1997	13/09/1996
Applicant		
SAGAMI CHEMICAL RESEARCH CENTER et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ **Certain claims were found unsearchable** (see Box I).

2. ☒ **Unity of invention is lacking** (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   ☐ filed with the international application.

   ☒ furnished by the applicant separately from the international application,

      ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   ☐ Transcribed by this Authority

4 With regard to the **title,**

   ☒ the text is approved as submitted by the applicant

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38 2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority

[illegible] suggested by the abstract

   ☐ because the applicant failed to suggest a figure

   ☐ because this figure better characterizes the invention

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 97/03239

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annex

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ [illegible] accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 10 and 19 and protein relating to SEQ ID No 1

2. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 11 and 20 and protein relating to SEQ ID No 2

3. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 12 and 21 and protein relating to SEQ ID No 3

4. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 13 and 22 and protein relating to SEQ ID No 4

5. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 14 and 23 and protein relating to SEQ ID No 5

6. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 15 and 24 and protein relating to SEQ ID No 6

7. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 16 and 25 and protein relating to SEQ ID No 7

8. Claims: Claims 1-4 in part

[illegible]

9. Claims: Claims 1-4 in part

DNAs relating to SEQ ID No 18 and 27 and protein relating to [illegible]

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/03239

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YOKOYAMA-KOBAYASHI M ET AL.: "A signal sequence detection system using secreted protease activity as an indicator" GENE., vol. 163, 1995, AMSTERDAM NL, pages 193-196, XP002053953 cited in the application see the whole document ---	1-4
Y	VON HEIJNE G: "A new method for predicting signal sequence cleavage sites" NUCLEIC ACIDS RESEARCH., vol. 14, 1986, OXFORD GB, pages 4683-4690, XP002053954 cited in the application see the whole document ---	1-4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

30 January 1998

Name and mailing address of the ISA
European Patent Office, P B 5818 Patentlaan 2
2280 HV Rijswijk

Authorized officer

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/03239

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TASHIRO K ET AL: "SIGNAL SEQUENCE TRAP: A CLONING STRATEGY FOR SECRETED PROTEINS AND TYPE I MEMBRANE PROTEINS" SCIENCE, vol. 261, 30 July 1993, pages 600-603, XP000673204 see the whole document ---	1-4
Y	WO 95 04158 A (UPJOHN CO ;HOOGWERF ARLENE J (US); LEDBETTER STEVEN R (US)) 9 February 1995 see page 51; claim 13 -----	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 97/03239

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9504158 A	09-02-95	AU 7368994 A	28-02-95
		EP 0708838 A	01-05-96
		JP 9504422 T	06-05-97

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/47

A2

(11) International Publication Number: **WO 98/11217**

(43) International Publication Date: 19 March 1998 (19.03.98)

(21) International Application Number: PCT/JP97/03239

(22) International Filing Date: 12 September 1997 (12.09.97)

(30) Priority Data:
8/243060 13 September 1996 (13.09.96) JP

(71) Applicants *(for all designated States except US)*: SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho, Meguro-ku, Tokyo 153 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229 (JP). SEKINE, Shingo [JP/JP]; 4-4-1, Nishi-Ohnuma, Sagamihara-shi, Kanagawa 229 (JP). YAMAGUCHI, Tomoko [JP/JP]; 5-13-11, Takasago, Katsushika-ku, Tokyo 125 (JP). KOBAYASHI, Midori [JP/JP]; 647-2, Chougo, Fujisawa-shi, Kanagawa 252 (JP).

(74) Agents: AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540 (JP).

(81) Designated States: AU, CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: HUMAN PROTEINS HAVING SECRETORY SIGNAL SEQUENCES AND DNAs ENCODING THESE PROTEINS

(57) Abstract

[Problems to be solved] To provide human proteins having secretory signal sequences and cDNAs encoding said proteins. [Means to solve the problems] Proteins containing any of the amino acid sequences represented by Sequence No. 1 to Sequence No. 9 and DNAs encoding said proteins exemplified by cDNAs containing any of the base sequences represented by Sequence No. 10 to Sequence No. 18. Said proteins can be provided by expressing cDNAs encoding human proteins having secretory signal sequences with verified secretory functions and recombinants of these human cDNAs.

FOR THE PURPOSES OF INFORMATION ONLY

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CH	[illegible]	**KG**	[illegible]	**NO**	[illegible]		
CI	[illegible]	**KP**	[illegible]	**NZ**	[illegible]		
CM	[illegible]	**KR**	[illegible]	**PL**	[illegible]		
CN	[illegible]	**KZ**	[illegible]	**PT**	[illegible]		
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DESCRIPTION

Human Proteins Having Secretory Signal Sequences and DNAs Encoding These Proteins

TECHNICAL FIELD

The present invention relates to human proteins having secretory signal sequences and DNAs encoding these proteins. The proteins of the present invention can be used as pharmaceuticals or as antigens for preparing antibodies against said proteins. The cDNAs of the present invention can be used as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be used as gene sources for large-scale production of the proteins encoded by said cDNAs.

BACKGROUND ART

Cells secrete many proteins outside the cells. These secretory proteins play important roles for the proliferation control, the differentiation induction, the material transportation, the biological protection, etc. in the cells. Different from intracellular proteins, the secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip to anticipate the potentialities as

thrombolytic agents, etc. have been currently utilized as

medicines. In addition, secretory proteins other than those described above have been undergoing clinical trials to develop as pharmaceuticals. Since it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes encoding them is expected to lead to the development of novel pharmaceuticals using these proteins.

Heretofore, such a secretory protein has been obtained by a method comprising the isolation and purification of the target protein from a large amount of the blood or a cell culture supernatant by using the biological activity as an indicator, determination of its primary structure followed by cloning of the corresponding cDNA on the basis of the information on the thus-obtained amino acid sequence, and production of the recombinant protein using said cDNA. However, the contents of the secretory proteins are generally so low that the isolation and purification are difficult in many cases. On the other hand, secretory proteins and type-I membrane proteins possess hydrophobic sequences, defined as the secretory signal sequences, consisting of about 20 amino acid residues at the amino acid termini (the N-termini). Therefore, the cloning of genes encoding the secretory proteins or type-I membrane proteins is expected to be performed by using the presence or the absence of these secretory signal sequences as indicators.

human proteins having secretory signal sequences and DNAs

encoding said proteins.

As the result of intensive studies, the present inventors were successful in cloning of cDNAs having secretory signal sequences from a human full-length cDNA bank, thereby completing the present invention. That is to say, the present invention provides proteins containing any of the amino acid sequences represented by Sequence No. 1 to Sequence No. 9 that are human proteins having secretory signal sequences. The present invention, also, provides DNAs encoding said proteins exemplified as cDNAs containing any of the base sequences represented by Sequence No. 10 to sequence No. 18.

Each of the proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc, a method for preparation of the peptide by the chemical synthesis on the basis of the amino acid sequence of the present invention, or a method for production with the recombinant DNA technology using the DNA encoding the human secretory protein of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For example, an in vitro expression can be achieved by preparation of an RNA by the in vitro transcription from a vector having a cDNA of the present invention, followed by the in vitro translation using this RNA as a template. Also, the recombination of the translation domain to a suitable expression vector by the method known in the art leads to the

and so on.

In the case in which a protein of the present invention is expressed by a microorganism such as *Escherichia coli*, the translation region of a cDNA of the present invention is constructed in an expression vector having an origin, a promoter, ribosome-binding site(s), cDNA-cloning site(s), a terminator, etc. that can be replicated in the microorganism and, after transformation of the host cells with said expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In that case, a maturation protein can be obtained by performing the expression with inserting an initiation codon in the translation region where the secretary signal sequence is removed. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion encoding said cDNA can be obtained by cleavage of said fusion protein with an appropriate protease.

In the case in which a protein of the present invention is secretory-expressed in animal cells, the protein of the present invention can be secretory-produced as a maturation protein outside the cells, when the translation region of said cDNA is subjected to recombination to an expression vector for animal cells that has a promoter for the animal cells, a splicing domain, a poly(A) addition site, etc., followed by transfection into the animal cells.

The proteins of the present invention include peptide

represented by Sequence No. 1 to Sequence No. 9. These

fragments can be used as antigens for preparation of the antibodies. Also, the proteins of the present invention are secreted in the form of maturation proteins outside the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore, many secretory proteins are subjected to the processing after the secretion to be converted to the active forms. These activated proteins or peptides shall come within the scope of the present invention. When glycosylation sites are present in the amino acid sequences, expression in appropriate animal cells affords glycosylated proteins. Therefore, these glycosylated proteins or peptides also shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs encoding the above-mentioned proteins. Said DNAs can be obtained using the method by chemical synthesis, the method by cDNA cloning, and so on.

Each of the cDNAs of the present invention can be cloned from, for example, a cDNA library of the human cell origin. The cDNA is synthesized using as a template a poly(A)$^+$ RNA extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation

using [illegible]

[Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170

(1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)] as illustrated in Examples in order to obtain a full-length clone in an effective manner.

The primary selection of a cDNA encoding a human protein having a secretory signal sequence is performed by the sequencing of a partial base sequence of the cDNA clone selected at random from the cDNA library, sequencing of the amino acid sequence encoded by the base sequence, and recognition of the presence or absence of hydrophobic site(s) in the resulting N-terminal amino acid sequence region. Next, the secondary selection is carried out by determination of the whole base sequence by the sequencing and the protein expression by the in vitro translation. The ascertainment of the cDNA of the present invention for encoding the protein having the secretory signal sequence is performed by using the signal sequence detection method [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)]. In other words, the ascertainment for the coding portion of the inserted cDNA fragment to function as a signal sequence is provided by fusing a cDNA fragment encoding the N-terminus of the target protein with a cDNA encoding the protease domain of urokinase and then expressing the resulting cDNA in COS7 cells to detect the urokinase activity in the cell culture medium.

The cDNAs of the present invention are characterized by

represented by Sequence No. 19 to Sequence No. 27. Table 1

summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

Table 1

Sequence Number	HP Number	Cells	Number of Bases	Number of Amino Acid Residues
1. 10. 19	HP00658	HT-1080	1296	154
2. 11. 20	HP00714	KB	3311	315
3. 12. 21	HP00876	Stomach cancer	1152	158
4. 13. 22	HP01134	Liver	1749	376
5. 14. 23	HP10029	KB	988	173
6. 15. 24	HP10189	KB	390	93
7. 16. 25	HP10269	U937	4667	1172
8. 17. 26	HP10298	Stomach cancer	1086	122
9. 18. 27	HP10368	Stomach cancer	866	175

Hereupon, the same clone as any of the cDNAs of the present invention can be easily obtained by screening of the cDNA library constructed from the cell line or the human tissue employed in the present invention, by the use of an oligonucleotide probe synthesized on the basis of the corresponding cDNA base sequence depicted in Sequence No. 19 to Sequence No. 27.

difference is frequently observed in human genes. Therefore, any cDNA that is subjected to insertion or deletion of one or

plural nucleotides and/or substitution with other nucleotides in Sequence No. 10 to Sequence No. 27 shall come within the scope of the present invention.

In a similar manner, any protein that is produced by these modifications comprising insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides shall come within the scope of the present invention, as far as said protein possesses the activity of the corresponding protein having the amino acid sequence represented by Sequence No. 1 to Sequence No. 9.

The cDNAs of the present invention include cDNA fragments (more than 10 bp) containing any partial base sequence of the base sequence represented by Sequence No. 10 to No. 18 or of the base sequence represented by Sequence No. 19 to No. 27. For example, as illustrated in Examples, the portion encoding the secretory signal sequence can be employed as means to secrete an optionally selected protein outside the cells by fusing with a cDNA encoding another protein. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA fragments can be used as the probes for the gene diagnosis.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: A figure depicting the structure of the secretory signal sequence detection vector pSSD3.

Figure 2: A figure depicting the construction of the

Figure [illegible]

hydrophobicity/hydrophilicity profile of the protein encoded

by clone HP00685.

Figure 4: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP00714.

Figure 5: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP00876.

Figure 6: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01134.

Figure 7: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10029.

Figure 8: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10189.

Figure 9: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10269.

Figure 10: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10298.

Figure 11: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10368.

EXAMPLE

The present invention is embodied in more detail by the

following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from Takara Shuzo Co., Ltd. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Preparation of Poly(A)$^+$ RNA

The fibrosarcoma cell line HT-1080 (ATCC CCL 121), the epidermoid carcinoma cell line KB (ATCC CRL 17), the histiocyte lymphoma cell line U937 (ATCC CRL 1593) stimulated by phorbol esters, tissues of stomach cancer delivered by the operation, and liver were used for human cells to extract mRNAs. Each of the cell lines was cultured by a conventional procedure.

After about 1 g of human tissues was homogenized in 20 ml of a 5.5 M guanidinium thiocyanate solution, total mRNAs were prepared in accordance with the literature [Okayama, H. et al., "Methods in Enzymology" Vol. 164, Academic Press, 1987]. These mRNAs were subjected to chromatography using an oligo(dT)-cellulose column washed with 20 mM Tris-

above-mentioned literature.

(2) Construction of cDNA Library

To a solution of 10 μg of the above-mentioned poly(A)$^+$ RNA in 100 mM Tris-hydrochloric acid buffer solution (pH 8) was added one unit of an RNase-free, bacterium-origin alkaline phosphatase and the resulting solution was allowed to react at 37°C for one hour. After the reaction solution underwent the phenol extraction followed by the ethanol precipitation, the obtained pellets were dissolved in a mixed solution of 50 mM sodium acetate (pH 6), 1 mM EDTA, 0.1% 2-mercaptoethanol, and 0.01% Triton X-100. Thereto was added one unit of a tobacco-origin pyrophosphatase (Epicenter Technologies) and the resulting solution at a total volume of 100 μl was allowed to react at 37°C for one hour. After the reaction solution underwent the phenol extraction followed by the ethanol precipitation, the thus-obtained pellets were dissolved in water to obtain a decapped poly(A)$^+$ RNA solution.

To a solution of the decapped poly(A)$^+$ RNA and 3 nmol of a DNA-RNA chimeric oligonucleotide (5'-dG-dG-dG-dG-dA-dA-dT-dT-dC-dG-dA-G-G-A-3') in a mixed aqueous solution of 50 mM Tris-hydrochloric acid buffer solution (pH 7.5), 0.5 mM ATP, 5 mM $MgCl_2$, 10 mM 2-mercaptoethanol, and 25% polyethylene glycol were added 50 units of T4 RNA ligase and the resulting solution at a total volume of 30 μl was allowed to react at 20°C for 12 hours. After the reaction solution underwent the phenol extraction followed by the ethanol precipitation, the

chimeric cap-capped poly(A)$^+$ RNA.

After the vector pKA1 developed by the present inventors (Japanese Patent Kokai Publication No. 1992-117292) was digested with KpnI, an about 60-dT tail was inserted by a terminal transferase. This product was digested with EcoRV to remove the dT tail at one side and the resulting molecule was used as a vectorial primer.

After 6 μg of the previously-prepared chimeric oligo-capped poly(A)$^+$ RNA was annealed with 1.2 μg of the vectorial primer, the product was dissolved in a mixed solution of 50 mM Tris-hydrochloric acid buffer solution (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 10 mM dithiothreitol, and 1.25 mM dNTP (dATP + dCTP + dGTP + dTTP), mixed with 200 units of a reverse transferase (GIBCO-BRL), and the resulting solution at a total volume of 20 μl was allowed to react at 42°C for one hour. After the reaction solution underwent the phenol extraction followed by the ethanol precipitation, the thus-obtained pellets were dissolved in a mixed solution of 50 mM Tris-hydrochloric acid buffer solution (pH 7.5), 100 mM NaCl, 10 mM $MgCl_2$, and 1 mM dithiothreitol. Thereto were added 100 units of EcoRI and the resulting solution at a total volume of 20 μl was allowed to react at 37°C for one hour. After the reaction solution underwent the phenol extraction followed by the ethanol precipitation, the obtained pellets were dissolved in a mixed solution of 20 mM Tris-hydrochloric acid buffer solution (pH 7.5), 100 mM KCl, 4 mM $MgCl_2$, 10 mM

resulting solution was allowed to react at 16°C for 15 hours.

To the reaction solution were added 2 µl of 2 mM dNTP, 4 units of *Escherichia coli* DNA polymerase I, and 0.1 unit of *Escherichia coli* DNase H and the resulting solution was allowed to react at 12°C for one hour and then at 22°C for one hour.

Next, the cDNA-synthesis reaction solution was used to transform *Escherichia coli* DH12S (GIBCO-BRL). The transformation was carried out by the electroporation method. A portion of the transformant was inoculated on a 2xYT agar culture medium containing 100 µg/ml ampicillin, which was incubated at 37°C overnight. A colony grown on the culture medium was randomly picked up and inoculated on 2 ml of the 2xYT culture medium containing 100 µg/ml ampicillin, which was incubated at 37°C overnight. The culture medium was centrifuged to separate the cells, from which a plasmid DNA was prepared by the alkaline lysis method. After the plasmid DNA was double-digested with EcoRI and NotI, the product was subjected to 0.8% agarose gel electrophoresis to determine the size of the cDNA insert. In addition, by the use of the obtained plasmid as a template, the sequence reaction using M13 universal primer labeled with a fluorescent dye and Taq polymerase (a kit of Applied Biosystems Inc.) was carried out and the product was analyzed by a fluorescent DNA-sequencer (Applied Biosystems Inc.) to determine the base sequence of the cDNA 5'-terminal of about 400 bp. The sequence data were filed as a homo-protein cDNA bank data base.

The base sequence registered in the homo-protein cDNA

bank was converted to three frames of amino acid sequences and the presence or absence of an open reading frame (ORF) beginning from the initiation codon. Then, the selection was made for the presence of a signal sequence that is characteristic to a secretory protein at the N-terminal of the portion encoded by ORF. These clones were sequenced from the both 5′ and 3′ directions by using the deletion method to determine the whole base sequence. The hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by ORF by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Bio. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. In the case in which there is not a hydrophobic region of putative transmembrane domain(s) in the amino acid sequence of an encoded protein, this protein was considered as a membrane protein that did not possess a secretory protein or transmembrane domain(s).

(4) Construction of Secretory Signal Detection Vector pSSD3

One microgram of pSSD1 carrying the SV40 promoter and a cDNA encoding the protease domain of urokinase [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)] was digested with 5 units of BglII and 5 units of EcoRV. Then, after dephosphorylation at the 5′ terminal by the CIP treatment, a DNA fragment of about 4.2 kbp was purified by cutting off from the gel of agarose gel electrophoresis.

phosphorylated by T4 polynucleotide kinase. After annealing

of the both linkers, followed by ligation with the previously-prepared pSSD1 fragment by T4 DNA ligase, *Escherichia coli* JM109 was transformed. A plasmid pSSD3 was prepared from the transformant and the objective recombinant was confirmed by the determination of the base sequence of the linker-inserted fragment. Figure 1 illustrates the structure of the thus-obtained plasmid. The present plasmid vector carries three types of blunt-end formation restriction enzyme sites, SmaI, PmaCI, and EcoRV. Since these cleavage sites are positioned in succession at an interval of 7 bp, selection of an appropriate site in combination of three types of frames for the inserting cDNA allows to construct a vector expressing a fusion protein.

(5) Functional Verification of Secretory Signal Sequence

Whether the N-terminal hydrophobic region in the secretory protein clone candidate obtained in the above-mentioned steps functions as the secretory signal sequence was verified by the method described in the literature [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)]. First, the plasmid containing the target cDNA was cleaved at an appropriate restriction enzyme site that existed at the downstream from the portion expected for encoding the secretory signal sequence. In the case in which this restriction enzyme site was a protruding 5'-terminus, the site was blunt-ended by the Klenow treatment. Digestion with HindIII was further carried out and a DNA fragment containing

[illegible]

gel electrophoresis. This fragment was inserted between the

pSSD3 HindIII site and a restriction enzyme site selected so as to match with the urokinase-coding frame, thereby constructing a vector expressing a fusion protein of the secretory signal portion of the target cDNA and the urokinase protease domain (refer to Figure 2).

After *Escherichia coli* (host: JM109) bearing the fusion-protein expression vector was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 μg/ml ampicillin, the helper phage M13KO7 (50 μl) was added and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 μl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE). Also, there was used as a control a suspension of single-stranded particles prepared in the same manner from the vector pKA1-UPA containing pSSD3 and a full-length cDNA of urokinase [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)].

The simian-kidney-origin culture cells, COS7, were incubated at 37°C in the presence of 5% CO_2 in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1×10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO_2. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and

hydrochloric acid (pH ... DMEM), ... were added 1 μl of the single-stranded phage suspension, 0.6 ml of the

DMEM culture medium, and 3 µl of TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO_2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO_2.

To 10 ml of 50 mM phosphate buffer solution (pH 7.4) containing 2% bovine fibrinogen (Miles Inc.), 0.5% agarose, and 1 mM potassium chloride were added 10 units of human thrombin (Mochida Pharmaceutical Co., Ltd.) and the resulting mixture was solidified in a plate of 9 cm in diameter to prepare a fibrin plate. Ten microliters of the culture supernatant of the transfected COS7 cells were spotted on the fibrin plate, which was incubated at 37°C for 15 hours. The diameter of the thus-obtained clear circle was taken as an index for the urokinase activity. Table 2 shows the restriction enzyme site used for cutting off the cDNA fragment from each clone, the restriction enzyme site used for cleavage of pSSD3, and the presence or absence of a clear circle. Except for pSSD3 used as the control, each of the samples formed a clear circle to identify that urokinase was secreted in the culture medium. That is to say, it is indicated that each of the cDNA fragments codes for the amino acid sequence that functions as the secretory signal sequence

Table 2

HP Number	Restriction Enzyme Site		Clear Circle
	cDNA*	Vector	
HP00658	HindIII (K)	SmaI	+
HP00714	PvuII	PmaCI	+
HP00876	NcoI (K)	PmaCI	+
HP01134	PmaCI	PmaCI	+
HP10029	ApaI (K)	SmaI	+
HP10189	BglI (K)	PmaCI	+
HP10269	PvuII	PmaCI	+
HP10298	HindIII (K)	PmaCI	+
HP10368	EcoRV	PmaCI	+
pKA1-UPA			+
pSSD3			-

* (K) means that cleavage with the restriction enzyme is followed by the Klenow treatment.

(6) Protein Synthesis by In Vitro Translation

The plasmid vector carrying the cDNA of the present invention was utilized for the in vitro transcription/translation by the T_NT rabbit reticulocyte lysate kit (Promega Biotec). In this case, [^{35}S]methionine was added and the expression product was labeled with the radioisotope. All reactions were carried out by following the protocols attached to the kit. Two micrograms of the plasmid was allowed to react at 30°C for 90 minutes in total 25 ml of reticulocyte lysate, 0.5 µl of the buffer solution (attached to the kit), 2 µl of an amino acid mixture (methionine-free),

2 μl (0.37 MBq/μl) of [^{35}S]methionine (Amersham Corporation), 0.5 μl of T7 RNA polymerase, and 20 U of RNasin. Also, the experiment in the presence of the membrane system was carried out by adding 2.5 μl of the dog pancreatic microsome fraction (Promega Biotec) into this reaction system. To 3 μl of the reaction solution was added 2 μl of an SDS sampling buffer (125 mM Tris-hydrochloric acid buffer solution, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting solution was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography. Table 3 shows the molecular weight of the in vitro translation product obtained from each of the clones in the presence/absence of the membrane microsome together with the calculated value of the molecular weight of the protein encoded by ORF of the cDNA.

Table 3

Sequence No.	HP Number	Calculated (Da)	In Vitro Translation Product (KDa)	
			Without Membrane System Added	With Membrane System Added*
1	HP00658	17,037	18	16
2	HP00714	37,106	47	-
3	HP00876	18,230	18	-
4	HP01134	42,947	42	49
5	HP10029	18,894	21	18
6	HP10189	9,113	12	-
7	HP10269	129,572	130	-
8	HP10298	13,161	16	-
9	HP10368	19,979	19	18

* - means "Not examined".

(7) Clone Examples

<HP00658> (Sequence Number 1, 10, 19)

Determination of the whole base sequence for the cDNA insert of clone HP00658 obtained from the human fibrosarcoma cell line HT-1080 cDNA libraries revealed the structure consisting of a 5'-non-translation region of 55 bp, an ORF of 465 bp, and a 3'-non-translation region of 776 bp. The ORF codes for a protein consisting of 154 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 3 depicts the

[illegible]

data base using the amino acid sequence encoded by the ORF

revealed that the N-terminal 63 amino acid residues thereof were completely identical with those in the RANTES protein (EMBL Accession No. 21121) except for one amino acid residue at position 7 (arginine in RANTES and alanine in the present protein), but the sequences in both proteins were completely different after position 64. Hereupon, RANTES consisted of 91 amino acid residues, whereas the present protein consisted of longer 154 amino acid residues. The in vitro translation resulted in the formation of a translation product of 18 kDa that was almost consistent with the molecular weight of 17,037 predicted from the ORF. In this case, the addition of the microsome resulted in the formation of a 16-kDa product in which the secretory signal sequence portion was putatively removed by cleavage. This result together with the result on pSSD3 verifies that the present protein possesses the secretory signal sequence. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site [von Heijne, G., Nucl. Acid Res. 14: 4683-4690 (1986)], allows to expect that the maturation protein starts from serine at position 24.

Comparison of the base sequences for the both proteins revealed that the base sequence from position 2 to position 325 in the present cDNA was deficient in the RANTES cDNA. It is considered that this deficiency resulted in induction of a frame shift to form an ORF of a different size. Some mutations were observed in other regions, wherein the

protein [Schall, T. J. et al., J. Immunol. 141: 1018-1025

(1988)], whereas the present cDNA was obtained from the fibrosarcoma cells. Accordingly, the present protein is considered to possess a different function from that of RANTES.

Furthermore, the search of GenBank using the base sequence of the present cDNA revealed that any EST possessing the homology of 90% or more was not found.

<HP00714> (Sequence Number 2, 11, 20)

Determination of the whole base sequence for the cDNA insert of clone HP00714 obtained from the human epidermoid carcinoma cell line KB cDNA libraries revealed the structure consisting of a 5'-non-translation region of 56 bp, an ORF of 948 bp, and a 3'-non-translation region of 2310 bp. The ORF codes for a protein consisting of 315 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 4 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 47 kDa that was somewhat larger than the molecular weight of 37,106 predicted from the ORF. Since the molecular weight of the human reticulocalbin analogous to the present protein is also larger by about 10 kDa than the molecular weight expected from the translation-product band on SDS-PAGE [Ozawa, M., J. Biochem. 117: 1113-1119 (1995)], the molecular weight difference in the present protein is considered to be

cleavage site, allows to expect that the maturation protein

starts from lysine at position 20. There is a possibility that the present protein exists in the endoplasmic reticulum because this protein possesses the C-terminal sequence HDEF analogous to KDEL, the signal motif sequence localized in the endoplasmic reticulum.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was analogous to the human reticulocalbin (GenBank Accession No. D42073). Table 4 indicates the comparison of the amino acid sequences between the human protein of the present invention (HP) and the human reticulocalbin (RC). - represents a gap, * represents an amino acid residue identical to that in the protein of the present invention, and . represents an amino acid residue analogous to that in the protein of the present invention. The both proteins possessed a homology of 60.5%.

Table 4

HP MDLRQFLMCLSLCTAFALSKPTEKKDR-VHHEPQLSDKVHNDAQSFDYDH

.*. * * . .*** .*.* *.....*... ..*.***.***

RC MARGGRGRRLGLALGLLLALVLAPRVLRAKPTVRKERVVRPDSELGERPPEDNQSFQYDH

HP DAFLGAEEAKTFDQLTPEESKERLGKIVSKIDGDKDGFVTVDELKDWIKFAQKRWIYEDV

.**** *..*********.**********..**.* *****..***.*** .***.*...*

RC EAFLGKEDSKTFDQLTPDESKERLGKIVDRIDNDGDGFVTTEELKTWIKRVQKRYIFDNV

HP ERQWKGHDLNEDGLVSWEEYKNATYGYVLDDP----DPDDGFNYKQMMVRDERRFKMADK

HP DGDDLIATKEEFTAFLHPEEYDYMKDIVVQETMEDIDKNADGFIDLEEYIGDMYSHDGNTL

```
   .***.**.**********...**.*** **.******.***.* .***.**.**..*.
RC NGDLTATREEFTAFLHPEEFEHMKEIVVLETLEDIDKNGDGFVDQDEYIADMFSHEENGP
HP EPEWVKTEREQFVEFRDKNRDGKMDKEETKDWILPSDYDHAEAEARHLVYESDQNKDGKL
   **.** .***** **** *.***.**.*... **** *****.**********.***.**
RC EPDWVLSEREQFNEFRDLNKDGKLDKDEIRHWILPQDYDHAQAEARHLVYESDKNKDEKL
HP TKEEIVDKYDLFVGSQATDFGEALVR-HDEF
   *****.....*******..**.*..  ***.
RC TKEEILENWNMFVGSQATNYGEDLTKNHDEL
```

Furthermore, the search of GenBank using the base sequence of the present cDNA revealed that there existed some ESTs possessing the homology of 90% or more and containing the initiation codon (for example, Accession No. F3872), but any of the sequences thereof did not allow to predict the present protein.

Reticulocalbin is a protein localized on the membrane surface of the endoplasmic reticulum and has been considered to participate in the protein folding. Accordingly, the protein of the present invention is considered to be applicable to the folding process of recombinant proteins.

<HP00876> (Sequence Number 3, 12, 21)

Determination of the whole base sequence for the cDNA insert of clone HP0876 obtained from the human stomach cancer cDNA libraries revealed the structure consisting of a 5'-non-translation region of 146 bp, an ORF of 477 bp, and a 3'-non-translation region of 529 bp. The ORF codes for a protein

[illegible] terminal. Figure 5 depicts the hydrophobicity/hydrophilicity

profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 18 kDa that was almost consistent with the molecular weight of 18,230 predicted from the ORF. In this case, the addition of the microsome resulted in the formation of a 16-kDa product in which the secretory signal sequence portion was putatively removed by cleavage. This result together with the result on pSSD3 verifies that the present protein possesses the secretory signal. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation protein starts from glycine at position 18 or aspartic acid at position 23.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was analogous to several type-C lectins. As an example, Table 5 indicates the comparison of the amino acid sequences between the human protein of the present invention (HP) and the rattlesnake lectin (CL) (Swiss-PROT Accession No. P21963). - represents a gap, * represents an amino acid residue identical to that in the protein of the present invention, and . represents an amino acid residue analogous to that in the protein of the present invention. The both proteins possessed a homology of 35.3%.

Table 5

```
HP MASRSMRLLLLLSCLAKTGVLGDIIMRPSCAPGWFYHKSNCYGYFRKLRNWSDAELECQS
                                    .*. .*.  .. **  *..*..*.***. *..
CL                                  NNCPLDWLPMNGLCYKIFNQLKTWEDAEMFCRK
HP YGNGAHLASILSLKEASTIAEYISGYQRSQ-PIWIGLHDPQKRQQWQWIDGAMYLYRSWS
   * * ****. .  *. .******.*...* .****.* .*  *.*.* .  * .*.
CL YKPGCHLASFHRYGESLEIAEYISDYHKGQENVWIGLRDKKKDFSWEWTDRSCTDYLTWD
HP GKSMGG--NKH-CAEMSSNNNFLTWSSNECNKRQHFLCKYRP
   . .  **. *.*. * ... *... *.... ***...
CL KNQPDHYQNKEFCVELVSLTGYRLWNDQVCESKDAFLCQCKF
```

Furthermore, the search of GenBank using the base sequence of the present cDNA revealed that any EST possessing the homology of 90% or more was not found.

After 1 μg of the plasmid pHP00876 was digested with 20 units of PvuII, the product was subjected to 1% agarose gel electrophoresis and an about 700-bp DNA fragment was cut off from the gel. Next, 1 μg of pET-21a (Novagen) was digested with 20 units of NheI, the product was subjected to the Klenow treatment followed by 1% agarose gel electrophoresis and an about 5.4-kbp DNA fragment was cut off from the gel. After ligation of the vector fragment and the cDNA fragment using a ligation kit, *Escherichia coli* BL21 (DE3) (Novagen) was transformed. A plasmid pET876 was prepared from the

vector expresses a protein in which methionine-alanine was

inserted before a protein starting from serine at position 29 in the protein encoded by the clone HP00876.

A suspension of pET876/BL21 (DE3) in 5 ml of the LB culture medium containing 100 μg/ml ampicillin was incubated in a shaker at 37°C and isopropylthiogalactoside was added to make 1 mM when A_{600} reached to about 0.5. After the incubation was continued at 37°C for 6 hours, cells were collected by centrifugation and suspended in 25 ml of a column buffer solution for the amylose column (10 mM Tris-hydrochloric acid, pH 7.4, 200 mM NaCl, and 1 mM EDTA). The resulting suspension was sonicated and then the insoluble fraction was subjected to SDS-polyacrylamide electrophoresis to identify a band originating from the expression of the present vector at a position of about 14 kDa.

Since lectins recognize and then bind to sugar chains, lectins are useful as sugar-chain detection reagents and as affinity carriers for purification of glycoproteins. In addition, extracellular secretory lectins play important roles also in intercellular signal transduction and thereby are useful as medicines.

<HP01134> (Sequence Number 4, 13, 22)

Determination of the whole base sequence for the cDNA insert of clone HP01134 obtained from the human liver cDNA libraries revealed the structure consisting of a 5'-non-translation region of 116 bp, an ORF of 1131 bp, and a 3'-non-translation region of 502 bp. The ORF codes for a protein

terminal. Figure 6 depicts the hydrophobicity/hydrophilicity

profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 42 kDa that was almost consistent with the molecular weight of 42,947 predicted from the ORF. In this case, the addition of the microsome resulted in the formation of a 49-kDa product in which a sugar chain was putatively added by N-glycosylation after the secretion. Hereupon, there exist in the amino acid sequence of this protein four possible N-glycosylation sites (Asn-Gly-Thr at position 91, Asn-Glu-Thr at position 167, Asn-Thr-Ser at position 263, and Asn-Lys-Thr at position 272). The above result together with the result on pSSD3 verifies that the present protein possesses the secretory signal. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation protein starts from alanine at position 17 or valine at position 18.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was analogous to several cysteine proteinases. As an example, Table 6 indicates the comparison of the amino acid sequences between the human protein of the present invention (HP) and the tangerine cysteine proteinase (CP) (GenBank Accession No. Z47793). - represents a gap, * represents an amino acid residue identical to that in the protein of the present invention, and . represents an amino acid residue analogous

region of 286 amino acid residues.

Table 6

```
HP                                          MVWKVAVFLSVALGIGAVPIDDPEDGGKH
                                                  * **   ** .. *. .
CP MTRLASGVLITLLVALAGIADGSRDIAGDILKLPSEAYRFFHNGGGGAKVNDDDDSVGTR
HP WVVIVAGSNGWYNYRHQADACHAYQIIHRNGIPDEQIVVMMYDDIAYSEDNPTPGIVINR
   *. *. . *****. . ******* *****. . . . *.  **. *. *. ******. . *. ** **. . **.
CP WAVLLAGSNGFWNYRHQADICHAYQLLRKGGLKDENIIVFMYDDIAFNEENPRPGVIINH
HP PNGTDVYQGVPKDYTGEDVTPQNFLAVLRGDAEAVKGIGSGKVLKSGPQDHVFIYFTDHG
   *. *. ***. ********** . . *. **.  *.  . *. . * *****. . ***. **. **. . . ***
CP PHGDDVYKGVPKDYTGEDVTVEKFFAVVLGNKTALTG-GSGKVVDSGPNDHIFIFYSDHG
HP STGILVFPNED-LHVKDLNETIHYMYKHKMYRKMVFYIEACESGSMMN-HLPDNINVYAT
   . . *. * . *. .  . . . . * . . . .  . .  *. . . ***. *******. . .  * . . . *. ***
CP GPGVLGMPTSRYIYADELIDVLKKKHASGNYKSLVFYLEACESGSIFEGLLLEGLNIYAT
HP TAANPRESSYACYY----DEKRSTY---LGDWYSVNWMEDSDVEDLTKETLHKQYHLVKS
   **. *.  ***. .  *.      . . . *   *** **. . ******. . . * . ****. **. ***.
CP TASNAEESSWGTYCPGEIPGPPPEYSTCLGDLYSIAWMEDSDIHNLRTETLHQQYELVKT
HP HT-----NTSHVMQYGNKTISTMKVMQFQGMKRKASSPVPLPPVTHLDLTPSPDVPLTIM
   .*      . *******. . .*. . . . * 
CP RTASYNSYGSHVMQYGDIGLSKNNLFTYLGTNPANDNYTFVDENSLRPASKAVNQRDADL
```

Furthermore, the search of GenBank using the base sequence of the present cDNA revealed that there existed some ESTs possessing the homology of 90% or more (for example,

identified.

Extracellular secretory proteases possess a variety of physiological functions and thereby are useful as medicines. In addition, the proteases have been utilized as research reagents for the structure analysis of proteins by restricted degradation and so on.

<HP10029> (Sequence Number 5, 14, 23)

Determination of the whole base sequence for the cDNA insert of clone HP10029 obtained from the human epidermoid carcinoma cell line KB cDNA libraries revealed the structure consisting of a 5'-non-translation region of 8 bp, an ORF of 522 bp, and a 3'-non-translation region of 458 bp. The ORF codes for a protein consisting of 173 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 7 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 21 kDa that was almost consistent with the molecular weight of 18,894 predicted from the ORF. In this case, the addition of the microsome resulted in the formation of a 18-kDa product in which the secretory signal sequence portion was putatively removed by cleavage. This result together with the result on pSSD3 verifies that the present protein possesses the secretory signal sequence. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation

endoplasmic reticulum because this protein possesses the C-

terminal sequence RTEL analogous to KDEL, the signal motif sequence localized in the endoplasmic reticulum.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was not homologous with any of known proteins. Hereupon, the search of GenBank using the base sequence revealed that there existed some ESTs possessing the homology of 90% or more (for example, Accession No. H87021), but they were shorter than the present cDNA and any molecule containing the initiation codon was not identified.

<HP10189> (Sequence Number 6, 15, 24)

Determination of the whole base sequence for the cDNA insert of clone HP10189 obtained from the human epidermoid carcinoma cell line KB cDNA libraries revealed the structure consisting of a 5'-non-translation region of 101 bp, an ORF of 222 bp, and a 3'-non-translation region of 67 bp. The ORF codes for a protein consisting of 73 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 8 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 10 kDa that was almost consistent with the molecular weight of 9,113 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation

sequence of the present protein revealed that the protein was

not homologous with any of known proteins. Hereupon, the search of GenBank using the base sequence revealed that there existed some ESTs possessing the homology of 90% or more and containing the initiation codon (for example, Accession No. N56270), but a frame shift had occurred and the same ORF as that in the present cDNA was not identified.

<HP10269> (Sequence Number 7, 16, 25)

Determination of the whole base sequence for the cDNA insert of clone HP10269 obtained from the human lymphoma cell line U937 cDNA libraries revealed the structure consisting of a 5'-non-translation region of 753 bp, an ORF of 351 bp, and a 3'-non-translation region of 395 bp. The ORF codes for a protein consisting of 1172 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 9 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 130 kDa that was almost consistent with the molecular weight of 129,571 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation protein starts from glutamine at position 18.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was analogous to the B3 chain of laminin S. Table 7 indicates the

human laminin S (B3) (GenBank Accession No. L25541)

Table 7

Amino Acid Residue Number	HP	B3
124	Gln	Arg
269	Pro	Deficient
388	Pro	Ala
426	Gln	Arg
427	Gly	Arg
439	Arg	Deficient
441	Asp	Glu
603	Arg	Pro
815	Gly	Ala

Comparison of the base sequence of the present cDNA and the base sequence described in the data base reveals that the 5'-terminus in the present cDNA is longer by 600 or more bp and the 81-bp 5'-terminus in the base sequence described in the data base is not consistent at all with the base sequence of the present cDNA. Accordingly, the both proteins originate from different mRNAs.

As an extracellular matrix, laminin deeply participates in the proliferation and differentiation of cells. Accordingly, laminin has been employed as an additive for the cell culture and so on.

<HP10298> (Sequence Number 8, 17, 26)

Determination of the whole base sequence for the cDNA

5'-non-translation region of 137 bp, an ORF of 369 bp, and a

3'-non-translation region of 580 bp. The ORF codes for a protein consisting of 122 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 10 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 16 kDa that was almost consistent with the molecular weight of 13,161 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation protein starts from leucine at position 18. There is also a possibility that the present protein possessing the hydrophobic C-terminal sequence of about 20 amino acid residues binds to the membrane via this portion.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was not homologous with any of known proteins. Hereupon, the search of GenBank using the base sequence revealed that there existed some ESTs possessing the homology of 90% or more and containing the initiation codon (for example, Accession No. D78655), but many sequences were not distinct and the same ORF as that in the present cDNA was not identified.

<HP10368> (Sequence Number 9, 18, 27)

Determination of the whole base sequence for the cDNA insert of clone HP10368 obtained from the human stomach

3'-non-translation region of 266 bp. The ORF codes for a

protein consisting of 175 amino acid residues with a hydrophobic region of a putative secretory signal sequence at the N-terminal. Figure 11 depicts the hydrophobicity/hydrophilicity profile of the present protein obtained by the Kyte-Doolittle method. The in vitro translation resulted in the formation of a translation product of 20 kDa that was almost consistent with the molecular weight of 19,979 predicted from the ORF. In this case, the addition of the microsome resulted in the formation of a 19-kDa product in which the secretory signal sequence portion was putatively removed by cleavage. This result together with the result on pSSD3 verifies that the present protein possesses the secretory signal. Application of the (-3,-1) rule, a method for predicting the signal sequence cleavage site, allows to expect that the maturation protein starts from leucine at position 19 or arginine at position 21. There is a possibility that the present protein exists in the endoplasmic reticulum because this protein possesses the C-terminal sequence KTEL analogous to KDEL, the signal motif sequence localized in the endoplasmic reticulum.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was not homologous with any of known proteins. Hereupon, the search of GenBank using the base sequence revealed that there existed some ESTs possessing the homology of 90% or more and containing the initiation codon (for example, Accession No.

INDUSTRIAL APPLICATION

The present invention provides human proteins having secretory signal sequences and cDNAs encoding said proteins. All of the proteins of the present invention are putative proteins controlling the proliferation and differentiation of the cells, because said proteins are secreted outside the cells and exist in the extracellular liquid or on the cell membrane surface. Therefore, the proteins of the present invention can be used as pharmaceuticals or as antigens for preparing antibodies against said proteins. Furthermore, said DNAs can be used for the expression of large amounts of said proteins.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein

preferentially expressed (either constitutively or at a

particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodiesusing DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune

protein (or its receptor) in biological fluids; as markers

for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such

source and use as a source of carbohydrate. In such cases

the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/DifferentiationActivity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in

Associates and Wiley-Interscience (Chapter 3, In Vitro assays

for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Po lyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human

U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark,S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are

severe combined immunodeficiency (SCID)), e.g., in regulating

(up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial orfungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ

Using the proteins of the invention it may also be

possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an

interaction of a B7 lymphocyte antigen with its natural

ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl.

Press, New York, 1989, pp. 846-847) can be used to determine

the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

immune responses, may also be useful in therapy.

Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte
antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function)

neuroblastoma, carcinoma) transfected with a nucleic acid

encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class IIα chain protein and an MHC class IIβ chain protein to thereby express MHC class I or MHC class II proteins on the

a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T

cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J.

Bertagnolli et al., Cellular Immunology 133:327-341, 1991;

Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559,

182:255-260, 1995; Nair et al., Journal of Virology

67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include,without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming

and proliferation of erythroid progenitor cells alone or in

combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among

various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY.

eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase

Another category of tissue regeneration activity that may

be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may

The protein of the present invention may also be useful

for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, vascular endothelium) tissue, or for promoting the growth of

cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

characterized by their ability to inhibit the release of

follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA

A protein of the present invention may have chemotactic

or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis)consist of assays

protein to induce the adhesion of one cell population to

another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result,such a protein is expected to be useful in treatment of various coagulation disorders (includinghereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include,

Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79

(1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement

Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein

et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of ytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

the invention may exhibit other anti-tumor activities. A

protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral

depression (including depressive disorders) and violent

behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

SEQUENCE LISTING

Sequence No.: 1

Sequence length: 154

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Fibrosarcoma

Cell line: HT-1080

Clone name: HP00658

Sequence description

Met	Lys	Val	Ser	Ala	Ala	Ala	Leu	Ala	Val	Ile	Leu	Ile	Ala	Thr	Ala
1				5				10						15	
Leu	Cys	Ala	Pro	Ala	Ser	Ala	Ser	Pro	Tyr	Ser	Ser	Asp	Thr	Thr	Pro
			20					25					30		
Cys	Cys	Phe	Ala	Tyr	Ile	Ala	Arg	Pro	Leu	Pro	Arg	Ala	His	Ile	Lys
		35					40					45			
Glu	Tyr	Phe	Tyr	Thr	Ser	Gly	Lys	Cys	Ser	Asn	Pro	Ala	Val	Val	His
	50					55					60				
Arg	Ser	Arg	Met	Pro	Lys	Arg	Glu	Gly	Gln	Gln	Val	Trp	Gln	Asp	Phe
65					70					75					80
Leu	Tyr	Asp	Ser	Arg	Leu	Asn	Lys	Gly	Lys	Leu	Cys	His	Pro	Lys	Glu
				85					90					95	

Gln Leu Phe Gly Asp Glu Leu Gly Trp Arg Val Leu Glu Pro Glu Leu

115 120 125

Thr Gln Ile Cys Leu Phe Leu Leu Ala Leu Val Leu Ala Trp Glu Ala

130 135 140

Ser Pro His Tyr Pro Thr Pro Pro Ala Pro

145 150

Sequence No.: 2

Sequence length: 315

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP00714

Sequence description

Met Asp Leu Arg Gln Phe Leu Met Cys Leu Ser Leu Cys Thr Ala Phe

1 5 10 15

Ala Leu Ser Lys Pro Thr Glu Lys Lys Asp Arg Val His His Glu Pro

20 25 30

Gln Leu Ser Asp Lys Val His Asn Asp Ala Gln Ser Phe Asp Tyr Asp

35 40 45

His Asp Ala Phe Leu Gly Ala Glu Glu Ala Lys Thr Phe Asp Gln Leu

50 55 60

Asp Gly Asp Lys Asp Gly Phe Val Thr Val Asp Glu Leu Lys Asp Trp

85 90 95

Ile Lys Phe Ala Gln Lys Arg Trp Ile Tyr Glu Asp Val Glu Arg Gln

100 105 110

Trp Lys Gly His Asp Leu Asn Glu Asp Gly Leu Val Ser Trp Glu Glu

115 120 125

Tyr Lys Asn Ala Thr Tyr Gly Tyr Val Leu Asp Asp Pro Asp Pro Asp

130 135 140

Asp Gly Phe Asn Tyr Lys Gln Met Met Val Arg Asp Glu Arg Arg Phe

145 150 155 160

Lys Met Ala Asp Lys Asp Gly Asp Leu Ile Ala Thr Lys Glu Glu Phe

165 170 175

Thr Ala Phe Leu His Pro Glu Glu Tyr Asp Tyr Met Lys Asp Ile Val

180 185 190

Val Gln Glu Thr Met Glu Asp Ile Asp Lys Asn Ala Asp Gly Phe Ile

195 200 205

Asp Leu Glu Glu Tyr Ile Gly Asp Met Tyr Ser His Asp Gly Asn Thr

210 215 220

Asp Glu Pro Glu Trp Val Lys Thr Glu Arg Glu Gln Phe Val Glu Phe

225 230 235 240

Arg Asp Lys Asn Arg Asp Gly Lys Met Asp Lys Glu Glu Thr Lys Asp

245 250 255

Trp Ile Leu Pro Ser Asp Tyr Asp His Ala Glu Ala Glu Ala Arg His

260 265 270

Leu Val Tyr Glu Ser Asp Gln Asn Lys Asp Gly Lys Leu Thr Lys Glu

275 280 285

Glu Ile Val Asp Lys Tyr Asp Leu Phe Val Gly Ser Gln Ala Thr Asp

305 310 315

Sequence No.: 3

Sequence length: 158

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP00876

Sequence description

Met	Ala	Ser	Arg	Ser	Met	Arg	Leu	Leu	Leu	Leu	Leu	Ser	Cys	Leu	Ala
1				5					10					15	
Lys	Thr	Gly	Val	Leu	Gly	Asp	Ile	Ile	Met	Arg	Pro	Ser	Cys	Ala	Pro
			20					25					30		
Gly	Trp	Phe	Tyr	His	Lys	Ser	Asn	Cys	Tyr	Gly	Tyr	Phe	Arg	Lys	Leu
		35					40					45			
Arg	Asn	Trp	Ser	Asp	Ala	Glu	Leu	Glu	Cys	Gln	Ser	Tyr	Gly	Asn	Gly
	50					55					60				
Ala	His	Leu	Ala	Ser	Ile	Leu	Ser	Leu	Lys	Glu	Ala	Ser	Thr	Ile	Ala
65					70					75					80
Glu	Tyr	Ile	Ser	Gly	Tyr	Gln	Arg	Ser	Gln	Pro	Ile	Trp	Ile	Gly	Leu
				85					90					95	
His	Asp	Pro	Gln	Lys	Arg	Gln	Gln	Trp	Gln	Trp	Ile	Asp	Gly	Ala	Met
			100					105					110		

Cys	Ala	Glu	Met	Ser	Ser	Asn	Asn	Asn	Phe	Leu	Thr	Trp	Ser	Ser	Asn

130 135 140

Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro

145 150 155

Sequence No.: 4

Sequence length: 376

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Liver

Clone name: HP01134

Sequence description

Met Val Trp Lys Val Ala Val Phe Leu Ser Val Ala Leu Gly Ile Gly

1 5 10 15

Ala Val Pro Ile Asp Asp Pro Glu Asp Gly Gly Lys His Trp Val Val

20 25 30

Ile Val Ala Gly Ser Asn Gly Trp Tyr Asn Tyr Arg His Gln Ala Asp

35 40 45

Ala Cys His Ala Tyr Gln Ile Ile His Arg Asn Gly Ile Pro Asp Glu

50 55 60

Gln Ile Val Val Met Met Tyr Asp Asp Ile Ala Tyr Ser Glu Asp Asn

65 70 75 80

Pro Thr Pro Gly Ile Val Ile Asn Arg Pro Asn Gly Thr Asp Val Tyr

[illegible]

100 105 110

Phe Leu Ala Val Leu Arg Gly Asp Ala Glu Ala Val Lys Gly Ile Gly
115 120 125
Ser Gly Lys Val Leu Lys Ser Gly Pro Gln Asp His Val Phe Ile Tyr
130 135 140
Phe Thr Asp His Gly Ser Thr Gly Ile Leu Val Phe Pro Asn Glu Asp
145 150 155 160
Leu His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His
165 170 175
Lys Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly
180 185 190
Ser Met Met Asn His Leu Pro Asp Asn Ile Asn Val Tyr Ala Thr Thr
195 200 205
Ala Ala Asn Pro Arg Glu Ser Ser Tyr Ala Cys Tyr Tyr Asp Glu Lys
210 215 220
Arg Ser Thr Tyr Leu Gly Asp Trp Tyr Ser Val Asn Trp Met Glu Asp
225 230 235 240
Ser Asp Val Glu Asp Leu Thr Lys Glu Thr Leu His Lys Gln Tyr His
245 250 255
Leu Val Lys Ser His Thr Asn Thr Ser His Val Met Gln Tyr Gly Asn
260 265 270
Lys Thr Ile Ser Thr Met Lys Val Met Gln Phe Gln Gly Met Lys Arg
275 280 285
Lys Ala Ser Ser Pro Val Pro Leu Pro Pro Val Thr His Leu Asp Leu
290 295 300
Thr Pro Ser Pro Asp Val Pro Leu Thr Ile Met Lys Arg Lys Leu Met
305 310 315 320

Arg His Leu Asp Tyr Glu Tyr Ala Leu Arg His Leu Tyr Val Leu Val

340 345 350

Asn Leu Cys Glu Lys Pro Tyr Pro Leu His Arg Ile Lys Leu Ser Met

355 360 365

Asp His Val Cys Leu Gly His Tyr

370 375

Sequence No.: 5

Sequence length: 173

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10029

Sequence description

Met Ala Ala Pro Ser Gly Gly Trp Asn Gly Val Arg Ala Ser Leu Trp

1 5 10 15

Ala Ala Leu Leu Leu Gly Ala Val Ala Leu Arg Pro Ala Glu Ala Val

20 25 30

Ser Glu Pro Thr Thr Val Ala Phe Asp Val Arg Pro Gly Gly Val Val

35 40 45

His Ser Phe Ser His Asn Val Gly Pro Gly Asp Lys Tyr Thr Cys Met

50 55 60

Leu Gly Thr Ser Glu Asp His Gln His Phe Thr Cys Thr Ile Trp Arg

85 90 95

Pro Gln Gly Lys Ser Tyr Leu Tyr Phe Thr Gln Phe Lys Ala Glu Val

100 105 110

Arg Gly Ala Glu Ile Glu Tyr Ala Met Ala Tyr Ser Lys Ala Ala Phe

115 120 125

Glu Arg Glu Ser Asp Val Pro Leu Lys Thr Glu Glu Phe Glu Val Thr

130 135 140

Lys Thr Ala Val Ala His Arg Pro Gly Ala Phe Lys Ala Glu Leu Ser

145 150 155 160

Lys Leu Val Ile Val Ala Lys Ala Ser Arg Thr Glu Leu

165 170

Sequence No.: 6

Sequence length: 73

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10189

Sequence description

Met Gly Val Lys Leu Glu Ile Phe Arg Met Ile Ile Tyr Leu Thr Phe

1 5 10 15

Asp Val Ile Gln Arg Lys Arg Glu Leu Trp Pro Pro Glu Lys Leu Gln

35 40 45

Glu Ile Glu Glu Phe Lys Glu Arg Leu Arg Lys Arg Arg Glu Glu Lys

50 55 60

Leu Leu Arg Asp Ala Gln Gln Asn Ser

65 70

Sequence No.: 7

Sequence length: 1172

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Hypothetical: No

Original source:

Organism species: *Homo sapiens*

Cell kind: Histiocyte lymphoma

Cell line: U937

Clone name: HP10269

Sequence description

Met Arg Pro Phe Phe Leu Leu Cys Phe Ala Leu Pro Gly Leu Leu His

1 5 10 15

Ala Gln Gln Ala Cys Ser Arg Gly Ala Cys Tyr Pro Pro Val Gly Asp

20 25 30

Leu Leu Val Gly Arg Thr Arg Phe Leu Arg Ala Ser Ser Thr Cys Gly

35 40 45

Leu Thr Lys Pro Glu Thr Tyr Cys Thr Gln Tyr Gly Glu Trp Gln Met

50 55 60

Arg Val Glu Asn Val Ala Ser Ser Ser Gly Pro Met Arg Trp Trp Gln

85 90 95

Ser Gln Asn Asp Val Asn Pro Val Ser Leu Gln Leu Asp Leu Asp Arg

100 105 110

Arg Phe Gln Leu Gln Glu Val Met Met Glu Phe Gln Gly Pro Met Pro

115 120 125

Ala Gly Met Leu Ile Glu Arg Ser Ser Asp Phe Gly Lys Thr Trp Arg

130 135 140

Val Tyr Gln Tyr Leu Ala Ala Asp Cys Thr Ser Thr Phe Pro Arg Val

145 150 155 160

Arg Gln Gly Arg Pro Gln Ser Trp Gln Asp Val Arg Cys Gln Ser Leu

165 170 175

Pro Gln Arg Pro Asn Ala Arg Leu Asn Gly Gly Lys Val Gln Leu Asn

180 185 190

Leu Met Asp Leu Val Ser Gly Ile Pro Ala Thr Gln Ser Gln Lys Ile

195 200 205

Gln Glu Val Gly Glu Ile Thr Asn Leu Arg Val Asn Phe Thr Arg Leu

210 215 220

Ala Pro Val Pro Gln Arg Gly Tyr His Pro Pro Ser Ala Tyr Tyr Ala

225 230 235 240

Val Ser Gln Leu Arg Leu Gln Gly Ser Cys Phe Cys His Gly His Ala

245 250 255

Asp Arg Cys Ala Pro Lys Pro Gly Ala Ser Ala Gly Pro Ser Thr Ala

260 265 270

Val Gln Val His Asp Val Cys Val Cys Gln His Asn Thr Ala Gly Pro

275 280 285

Asn Cys Glu Arg Cys Ala Pro Phe Tyr Asn Asn Arg Pro Trp Arg Pro

305 310 315 320

His Ser Glu Thr Cys His Phe Asp Pro Ala Val Phe Ala Ala Ser Gln
325 330 335
Gly Ala Tyr Gly Gly Val Cys Asp Asn Cys Arg Asp His Thr Glu Gly
340 345 350
Lys Asn Cys Glu Arg Cys Gln Leu His Tyr Phe Arg Asn Arg Arg Pro
355 360 365
Gly Ala Ser Ile Gln Glu Thr Cys Ile Ser Cys Glu Cys Asp Pro Asp
370 375 380
Gly Ala Val Pro Gly Ala Pro Cys Asp Pro Val Thr Gly Gln Cys Val
385 390 395 400
Cys Lys Glu His Val Gln Gly Glu Arg Cys Asp Leu Cys Lys Pro Gly
405 410 415
Phe Thr Gly Leu Thr Tyr Ala Asn Pro Gln Gly Cys His Arg Cys Asp
420 425 430
Cys Asn Ile Leu Gly Ser Arg Arg Asp Met Pro Cys Asp Glu Glu Ser
435 440 445
Gly Arg Cys Leu Cys Leu Pro Asn Val Val Gly Pro Lys Cys Asp Gln
450 455 460
Cys Ala Pro Tyr His Trp Lys Leu Ala Ser Gly Gln Gly Cys Glu Pro
465 470 475 480
Cys Ala Cys Asp Pro His Asn Ser Leu Ser Pro Gln Cys Asn Gln Phe
485 490 495
Thr Gly Gln Cys Pro Cys Arg Glu Gly Phe Gly Gly Leu Met Cys Ser
500 505 510
Ala Ala Ala Ile Arg Gln Cys Pro Asp Arg Thr Tyr Gly Asp Val Ala
515 520 525

Gly Cys Asp Lys Ala Ser Gly Arg Cys Leu Cys Arg Pro Gly Leu Thr

545 550 555 560

Gly Pro Arg Cys Asp Gln Cys Gln Arg Gly Tyr Cys Asn Arg Tyr Pro

565 570 575

Val Cys Val Ala Cys His Pro Cys Phe Gln Thr Tyr Asp Ala Asp Leu

580 585 590

Arg Glu Gln Ala Leu Arg Phe Gly Arg Leu Arg Asn Ala Thr Ala Ser

595 600 605

Leu Trp Ser Gly Pro Gly Leu Glu Asp Arg Gly Leu Ala Ser Arg Ile

610 615 620

Leu Asp Ala Lys Ser Lys Ile Glu Gln Ile Arg Ala Val Leu Ser Ser

625 630 635 640

Pro Ala Val Thr Glu Gln Glu Val Ala Gln Val Ala Ser Ala Ile Leu

645 650 655

Ser Leu Arg Arg Thr Leu Gln Gly Leu Gln Leu Asp Leu Pro Leu Glu

660 665 670

Glu Glu Thr Leu Ser Leu Pro Arg Asp Leu Glu Ser Leu Asp Arg Ser

675 680 685

Phe Asn Gly Leu Leu Thr Met Tyr Gln Arg Lys Arg Glu Gln Phe Glu

690 695 700

Lys Ile Ser Ser Ala Asp Pro Ser Gly Ala Phe Arg Met Leu Ser Thr

705 710 715 720

Ala Tyr Glu Gln Ser Ala Gln Ala Ala Gln Gln Val Ser Asp Ser Ser

725 730 735

Arg Leu Leu Asp Gln Leu Arg Asp Ser Arg Arg Glu Ala Glu Arg Leu

740 745 750

Val Arg Gln Ala Gly Gly Gly Gly Gly Thr Gly Ser Pro Lys Leu Val

770 775 780

Asn Lys Leu Cys Gly Asn Ser Arg Gln Met Ala Cys Thr Pro Ile Ser
785 790 795 800

Cys Pro Gly Glu Leu Cys Pro Gln Asp Asn Gly Thr Ala Cys Gly Ser
805 810 815

Arg Cys Arg Gly Val Leu Pro Arg Ala Gly Gly Ala Phe Leu Met Ala
820 825 830

Gly Gln Val Ala Glu Gln Leu Arg Gly Phe Asn Ala Gln Leu Gln Arg
835 840 845

Thr Arg Gln Met Ile Arg Ala Ala Glu Glu Ser Ala Ser Gln Ile Gln
850 855 860

Ser Ser Ala Gln Arg Leu Glu Thr Gln Val Ser Ala Ser Arg Ser Gln
865 870 875 880

Met Glu Glu Asp Val Arg Arg Thr Arg Leu Leu Ile Gln Gln Val Arg
885 890 895

Asp Phe Leu Thr Asp Pro Asp Thr Asp Ala Ala Thr Ile Gln Glu Val
900 905 910

Ser Glu Ala Val Leu Ala Leu Trp Leu Pro Thr Asp Ser Ala Thr Val
915 920 925

Leu Gln Lys Met Asn Glu Ile Gln Ala Ile Ala Ala Arg Leu Pro Asn
930 935 940

Val Asp Leu Val Leu Ser Gln Thr Lys Gln Asp Ile Ala Arg Ala Arg
945 950 955 960

Arg Leu Gln Ala Glu Ala Glu Glu Ala Arg Ser Arg Ala His Ala Val
965 970 975

Glu Gly Gln Val Glu Asp Val Val Gly Asn Leu Arg Gln Gly Thr Val
980 985 990

Arg Leu Ile Gln Asp Arg Val Ala Glu Val Gln Gln Val Leu Arg Pro

1010 1015 1020

Ala Glu Lys Leu Val Thr Ser Met Thr Lys Gln Leu Gly Asp Phe Trp

1025 1030 1035 1040

Thr Arg Met Glu Glu Leu Arg His Gln Ala Arg Gln Gln Gly Ala Glu

1045 1050 1055

Ala Val Gln Ala Gln Gln Leu Ala Glu Gly Ala Ser Glu Gln Ala Leu

1060 1065 1070

Ser Ala Gln Glu Gly Phe Glu Arg Ile Lys Gln Lys Tyr Ala Glu Leu

1075 1080 1085

Lys Asp Arg Leu Gly Gln Ser Ser Met Leu Gly Glu Gln Gly Ala Arg

1090 1095 1100

Ile Gln Ser Val Lys Thr Glu Ala Glu Glu Leu Phe Gly Glu Thr Met

1105 1110 1115 1120

Glu Met Met Asp Arg Met Lys Asp Met Glu Leu Glu Leu Leu Arg Gly

1125 1130 1135

Ser Gln Ala Ile Met Leu Arg Ser Ala Asp Leu Thr Gly Leu Glu Lys

1140 1145 1150

Arg Val Glu Gln Ile Arg Asp His Ile Asn Gly Arg Val Leu Tyr Tyr

1155 1160 1165

Ala Thr Cys Lys

1170

Sequence No.: 8

Sequence length: 122

Sequence type: Amino acid

Topology: Linear

[illegible]

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP10298

Sequence description

Met Gly Leu Leu Leu Leu Val Pro Leu Leu Leu Leu Pro Gly Ser Tyr
1 5 10 15

Gly Leu Pro Phe Tyr Asn Gly Phe Tyr Tyr Ser Asn Ser Ala Asn Asp
20 25 30

Gln Asn Leu Gly Asn Gly His Gly Lys Asp Leu Leu Asn Gly Val Lys
35 40 45

Leu Val Val Glu Thr Pro Glu Glu Thr Leu Phe Thr Arg Ile Leu Thr
50 55 60

Val Gly Pro Gln Ser Leu Gly Ser Glu Ala Leu Ala Ser Pro Thr Arg
65 70 75 80

Arg Ala Ala Cys Thr Val Phe Thr Ala Thr Ala Ser Thr Arg Thr Trp
85 90 95

Gly Pro Pro Leu Pro His Ser Leu Thr Gly Cys Val Phe Ile Glu Trp
100 105 110

Phe Val Phe Pro Cys Gly Leu Glu Pro Phe
115 120

Sequence No.: 9

Sequence length: 175

Sequence type: Amino acid

Topology: Linear

Sequence kind: Protein

Original source

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP10368

Sequence description

Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser
1 5 10 15

Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp
20 25 30

Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp
35 40 45

Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys
50 55 60

Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu
65 70 75 80

Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu
85 90 95

Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu
100 105 110

Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile
115 120 125

Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg
130 135 140

Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu
145 150 155 160

Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu
165 170 175

Sequence length: 1.6

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Fibrosarcoma

Cell line: HT-1080

Clone name: HP00658

Sequence description

ATGAAGGTCT CCGCGGCAGC CCTCGCTGTC ATCCTCATTG CTACTGCCCT CTGCGCTCCT 60

GCATCTGCCT CCCCATATTC CTCGGACACC ACACCCTGCT GCTTTGCCTA CATTGCCCGC 120

CCACTGCCCC GTGCCCACAT CAAGGAGTAT TTCTACACCA GTGGCAAGTG CTCCAACCCA 180

GCAGTCGTCC ACAGGTCAAG GATGCCAAAG AGAGAGGGAC AGCAAGTCTG GCAGGATTTC 240

CTGTATGACT CCCGGCTGAA CAAGGGCAAG CTTTGTCACC CGAAAGAACC GCCAAGTGTG 300

TGCCAACCCA GAGAAGAAAT GGGTTCGGGA GTACATCAAC TCTTTGGAGA TGAGCTAGGA 360

TGGAGAGTCC TTGAACCTGA ACTTACACAA ATTTGCCTGT TTCTGCTTGC TCTTGTCCTA 420

GCTTGGGAGG CTTCCCCTCA CTATCCTACC CCACCCGCTC CT 462

Sequence No.: 11

Sequence length: 945

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP00714

Sequence description

ATGGACCTGC GACAGTTTCT TATGTGCCTG TCCCTGTGCA CAGCCTTTGC CTTGAGCAAA 60

CCCACAGAAA AGAAGGACCG TGTACATCAT GAGCCTCAGC TCAGTGACAA GGTTCACAAT 120

GATGCTCAGA GTTTTGATTA TGACCATGAT GCCTTCTTGG GTGCTGAAGA AGCAAAGACC 180

TTTGATCAGC TGACACCAGA AGAGAGCAAG GAAAGGCTTG GAAAGATTGT AAGTAAAATA 240

GATGGCGACA AGGACGGGTT TGTCACTGTG GATGAGCTCA AAGACTGGAT TAAATTTGCA 300

CAAAAGCGCT GGATTTACGA GGATGTAGAG CGACAGTGGA AGGGGCATGA CCTCAATGAG 360

GACGGCCTCG TTTCCTGGGA GGAGTATAAA AATGCCACCT ACGGCTACGT TTTAGATGAT 420

CCAGATCCTG ATGATGGATT TAACTATAAA CAGATGATGG TTAGAGATGA GCGGAGGTTT 480

AAAATGGCAG ACAAGGATGG AGACCTCATT GCCACCAAGG AGGAGTTCAC AGCTTTCCTG 540

CACCCTGAGG AGTATGACTA CATGAAAGAT ATAGTAGTAC AGGAAACAAT GGAAGATATA 600

GATAAGAATG CTGATGGTTT CATTGATCTA GAAGAGTATA TTGGTGACAT GTACAGCCAT 660

GATGGGAATA CTGATGAGCC AGAATGGGTA AAGACAGAGC GAGAGCAGTT TGTTGAGTTT 720

CGGGATAAGA ACCGTGATGG GAAGATGGAC AAGGAAGAGA CCAAAGACTG GATCCTTCCC 780

TCAGACTATG ATCATGCAGA GGCAGAAGCC AGGCACCTGG TCTATGAATC AGACCAAAAC 840

AAGGATGGCA AGCTTACCAA GGAGGAGATC GTTGACAAGT ATGACTTATT TGTTGGCAGC 900

CAGGCCACAG ATTTTGGGGA GGCCTTAGTA CGGCATGATG AGTTC 945

Sequence No.: 12

Sequence length: 474

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Clone name: HP00876

Sequence description

ATGGCTTCCA GAAGCATGCG GCTGCTCCTA TTGCTGAGCT GCCTGGCCAA AACAGGAGTC 60

CTGGGTGATA TCATCATGAG ACCCAGCTGT GCTCCTGGAT GGTTTTACCA CAAGTCCAAT 120

TGCTATGGTT ACTTCAGGAA GCTGAGGAAC TGGTCTGATG CCGAGCTCGA GTGTCAGTCT 180

TACGGAAACG GAGCCCACCT GGCATCTATC CTGAGTTTAA AGGAAGCCAG CACCATAGCA 240

GAGTACATAA GTGGCTATCA GAGAAGCCAG CCGATATGGA TTGGCCTGCA CGACCCACAG 300

AAGAGGCAGC AGTGGCAGTG GATTGATGGG GCCATGTATC TGTACAGATC CTGGTCTGGC 360

AAGTCCATGG GTGGGAACAA GCACTGTGCT GAGATGAGCT CCAATAACAA CTTTTTAACT 420

TGGAGCAGCA ACGAATGCAA CAAGCGCCAA CACTTCCTGT GCAAGTACCG ACCA 474

Sequence No.: 13

Sequence length: 1128

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Liver

Clone name: HP01134

Sequence description

ATGGTTTGGA AAGTAGCTGT ATTCCTCAGT GTGGCCCTGG GCATTGGTGC CGTTCCTATA 60

GATGATCCTG AAGATGGAGG CAAGCACTGG GTGGTGATCG TGGCAGGTTC AAATGGCTGG 120

TATAATTATA GGCACCAGGC AGACGCGTGC CATGCCTACC AGATCATTCA CCGCAATGGG 180

ATTCCTGACG AACAGATCGT TGTGATGATG TACGATGACA TTGCTTACTC TGAAGACAAT 240

CCCACTCCAG GAATTGTGAT CAACAGGCCC AATGGCACAG ATGTCTATCA GGGAGTCCCG 300

[illegible] 480

CTTCATGTAA AGGACCTGAA TGAGACCATC CATTACATGT ACAAACACAA AATGTACCGA 540

AAGATGGTGT TCTACATTGA AGCCTGTGAG TCTGGGTCCA TGATGAACCA CCTGCCGGAT 600

AACATCAATG TTTATGCAAC TACTGCTGCC AACCCCAGAG AGTCGTCCTA CGCCTGTTAC 660

TATGATGAGA AGAGGTCCAC GTACCTGGGG GACTGGTACA GCGTCAACTG GATGGAAGAC 720

TCGGACGTGG AAGATCTGAC TAAAGAGACC CTGCACAAGC AGTACCACCT GGTAAAATCG 780

CACACCAACA CCAGCCACGT CATGCAGTAT GGAAACAAAA CAATCTCCAC CATGAAAGTG 840

ATGCAGTTTC AGGGTATGAA ACGCAAAGCC AGTTCTCCCG TCCCCCTACC TCCAGTCACA 900

CACCTTGACC TCACCCCCAG CCCTGATGTG CCTCTCACCA TCATGAAAAG GAAACTGATG 960

AACACCAATG ATCTGGAGGA GTCCAGGCAG CTCACGGAGG AGATCCAGCG GCATCTGGAT 1020

TACGAGTATG CGTTGAGACA TTTGTACGTG CTGGTCAACC TTTGTGAGAA GCCGTATCCG 1080

CTTCACAGGA TAAAATTGTC CATGGACCAC GTGTGCCTTG GTCACTAC 1128

Sequence No.: 14

Sequence length: 519

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10029

Sequence description

ATGGCGGCGC CCAGCGGAGG GTGGAACGGC GTCCGCGCGA GCTTGTGGGC CGCGCTGCTC 60

CTAGGGGCCG TGGCGCTGAG GCCGGCGGAG GCGGTGTCCG AGCCCACGAC CGTGGCGTTT 120

TATACGTGTA TGTTCACTTA CGCCTCTCAA GGAGGGACCA ATGAGCAATC GCAGATGAGC 180

CTGGGGACCA GCGAAGACCA CCAGCACTTC ACCTGCACCA TCTGGAGGCC CCAGGGGAAG 300

TCCTATCTGT ACTTCACACA GTTCAAGGCA GAGGTGCGGG GCGCTGAGAT TGAGTACGCC 360

ATGGCCTACT CTAAAGCCGC ATTTGAAAGG GAAAGTGATG TCCCTCTGAA AACTGAGGAA 420

TTTGAAGTGA CCAAAACAGC AGTGGCTCAC AGGCCCGGGG CATTCAAAGC TGAGCTGTCC 480

AAGCTGGTGA TTGTGGCCAA GGCATCGCGC ACTGAGCTG 519

Sequence No.: 15

Sequence length: 219

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10189

Sequence description

ATGGGGGTGA AGCTGGAGAT ATTTCGGATG ATAATCTACC TCACTTTCCC TGTGGCTATG 60

TTCTGGGTTT CCAATCAGGC CGAGTGGTTT GAGGACGATG TCATACAGCG CAAGAGGGAG 120

CTGTGGCCAC CTGAGAAGCT TCAAGAGATA GAGGAATTCA AAGAGAGGTT ACGGAAGCGG 180

CGGGAGGAGA AGCTCCTTCG CGACGCCCAG CAGAACTCC 219

Sequence No.: 16

Sequence length: 3516

Sequence type: Nucleic acid

Strandedness: Double

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Lymphoma

Cell line: U937

Clone name: HP10269

Sequence description

ATGAGACCAT TCTTCCTCTT GTGTTTTGCC CTGCCTGGCC TCCTGCATGC CCAACAAGCC 60

TGCTCCCGTG GGGCCTGCTA TCCACCTGTT GGGGACCTGC TTGTTGGGAG GACCCGGTTT 120

CTCCGAGCTT CATCTACCTG TGGACTGACC AAGCCTGAGA CCTACTGCAC CCAGTATGGC 180

GAGTGGCAGA TGAAATGCTG CAAGTGTGAC TCCAGGCAGC CTCACAACTA CTACAGTCAC 240

CGAGTAGAGA ATGTGGCTTC ATCCTCCGGC CCCATGCGCT GGTGGCAGTC CCAGAATGAT 300

GTGAACCCTG TCTCTCTGCA GCTGGACCTG GACAGGAGAT TCCAGCTTCA AGAAGTCATG 360

ATGGAGTTCC AGGGGCCCAT GCCTGCCGGC ATGCTGATTG AGCGCTCCTC AGACTTCGGT 420

AAGACCTGGC GAGTGTACCA GTACCTGGCT GCCGACTGCA CCTCCACCTT CCCTCGGGTC 480

CGCCAGGGTC GGCCTCAGAG CTGGCAGGAT GTTCGGTGCC AGTCCCTGCC TCAGAGGCCT 540

AATGCACGCC TAAATGGGGG GAAGGTCCAA CTTAACCTTA TGGATTTAGT GTCTGGGATT 600

CCAGCAACTC AAAGTCAAAA AATTCAAGAG GTGGGGGAGA TCACAAACTT GAGAGTCAAT 660

TTCACCAGGC TGGCCCCTGT GCCCCAAAGG GGCTACCACC CTCCCAGCGC CTACTATGCT 720

GTGTCCCAGC TCCGTCTGCA GGGGAGCTGC TTCTGTCACG GCCATGCTGA TCGCTGCGCA 780

CCCAAGCCTG GGGCCTCTGC AGGCCCCTCC ACCGCTGTGC AGGTCCACGA TGTCTGTGTC 840

TGCCAGCACA ACACTGCCGG CCCAAATTGT GAGCGCTGTG CACCCTTCTA CAACAACCGG 900

CCCTGGAGAC CGGCGGAGGG CCAGGACGCC CATGAATGCC AAAGGTGCGA CTGCAATGGG 960

CACTCAGAGA CATGTCACTT TGACCCCGCT GTGTTTGCCG CCAGCCAGGG GGCATATGGA 1020

GGTGTGTGTG ACAATTGCCG GGACCACACC GAAGGCAAGA ACTGTGAGCG GTGTCAGCTG 1080

CACTATTTCC GGAACCGGCG CCCGGGAGCT TCCATTCAGG AGACCTGCAT CTCCTGCGAG 1140

TGTGATCCGG ATGGGGCAGT GCCAGGGGCT CCCTGTGACC CAGTGACCGG GCAGTGTGTG 1200

TGCAAGGAGC ATGTGCAGGG AGAGCGCTGT GACCTATGCA AGCCGGGCTT CACTGGACTC 1260

[illegible] 48

AAATGTGACC AGTGTGCTCC CTACCACTGG AAGCTGGCCA GTGGCCAGGG CTGTGAACCG 1440

TGTGCCTGCG ACCCGCACAA CTCCCTCAGC CCACAGTGCA ACCAGTTCAC AGGGCAGTGC 1500

CCCTGTCGGG AAGGCTTTGG TGGCCTGATG TGCAGCGCTG CAGCCATCCG CCAGTGTCCA 1560

GACCGGACCT ATGGAGACGT GGCCACAGGA TGCCGAGCCT GTGACTGTGA TTTCCGGGGA 1620

ACAGAGGGCC CGGGCTGCGA CAAGGCATCA GGCCGCTGCC TCTGCCGCCC TGGCTTGACC 1680

GGGCCCCGCT GTGACCAGTG CCAGCGAGGC TACTGCAATC GCTACCCGGT GTGCGTGGCC 1740

TGCCACCCTT GCTTCCAGAC CTATGATGCG GACCTCCGGG AGCAGGCCCT GCGCTTTGGT 1800

AGACTCCGCA ATGCCACCGC CAGCCTGTGG TCAGGGCCTG GGCTGGAGGA CCGTGGCCTG 1860

GCCTCCCGGA TCCTAGATGC AAAGAGTAAG ATTGAGCAGA TCCGAGCAGT TCTCAGCAGC 1920

CCCGCAGTCA CAGAGCAGGA GGTGGCTCAG GTGGCCAGTG CCATCCTCTC CCTCAGGCGA 1980

ACTCTCCAGG GCCTGCAGCT GGATCTGCCC CTGGAGGAGG AGACGTTGTC CCTTCCGAGA 2040

GACCTGGAGA GTCTTGACAG AAGCTTCAAT GGTCTCCTTA CTATGTATCA GAGGAAGAGG 2100

GAGCAGTTTG AAAAAATAAG CAGTGCTGAT CCTTCAGGAG CCTTCCGGAT GCTGAGCACA 2160

GCCTACGAGC AGTCAGCCCA GGCTGCTCAG CAGGTCTCCG ACAGCTCGCG CCTTTTGGAC 2220

CAGCTCAGGG ACAGCCGGAG AGAGGCAGAG AGGCTGGTGC GGCAGGCGGG AGGAGGAGGA 2280

GGCACCGGCA GCCCCAAGCT TGTGGCCCTG AGGCTGGAGA TGTCTTCGTT GCCTGACCTG 2340

ACACCCACCT TCAACAAGCT CTGTGGCAAC TCCAGGCAGA TGGCTTGCAC CCCAATATCA 2400

TGCCCTGGTG AGCTATGTCC CCAAGACAAT GGCACAGCCT GTGGCTCCCG CTGCAGGGGT 2460

GTCCTTCCCA GGGCCGGTGG GGCCTTCTTG ATGGCGGGGC AGGTGGCTGA GCAGCTGCGG 2520

GGCTTCAATG CCCAGCTCCA GCGGACCAGG CAGATGATTA GGGCAGCCGA GGAATCTGCC 2580

TCACAGATTC AATCCAGTGC CCAGCGCTTG GAGACCCAGG TGAGCGCCAG CCGCTCCCAG 2640

ATGGAGGAAG ATGTCAGACG CACACGGCTC CTAATCCAGC AGGTCCGGGA CTTCCTAACA 2700

GACCCCGACA CTGATGCAGC CACTATCCAG GAGGTCAGCG AGGCCGTGCT GGCCCTGTGG 2760

CTGCCCACAG ACTCAGCTAC TGTTCTGCAG AAGATGAATG AGATCCAGGC CATTGCAGCC 2820

AGGCTCCCCA ACGTGGACTT GGTGCTGTCC CAGACCAAGC AGGACATTGC GCGTGCCCGC 2880

CGGTTGCAGG CTGAGGCTGA GGAAGCCAGG AGCCGAGCCC ATGCAGTGGA GGGCCAGGTG 2940

GAAGATGTGG TTGGGAACCT GCGGCAGGGG ACAGTGGCAC TGCAGGAAGC TCAGGACACC 3000

[illegible] 3120

ACACGGATGG AGGAGCTCCG CCACCAAGCC CGGCAGCAGG GGGCAGAGGC AGTCCAGGCC 3180

CAGCAGCTTG CGGAAGGTGC CAGCGAGCAG GCATTGAGTG CCCAAGAGGG ATTTGAGAGA 3240

ATAAAACAAA AGTATGCTGA GTTGAAGGAC CGGTTGGGTC AGAGTTCCAT GCTGGGTGAG 3300

CAGGGTGCCC GGATCCAGAG TGTGAAGACA GAGGCAGAGG AGCTGTTTGG GGAGACCATG 3360

GAGATGATGG ACAGGATGAA AGACATGGAG TTGGAGCTGC TGCGGGGCAG CCAGGCCATC 3420

ATGCTGCGCT CAGCGGACCT GACAGGACTG GAGAAGCGTG TGGAGCAGAT CCGTGACCAC 3480

ATCAATGGGC GCGTGCTCTA CTATGCCACC TGCAAG 3516

Sequence No.: 17

Sequence length: 366

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP10298

Sequence description

ATGGGCCTGT TGCTCCTGGT CCCATTGCTC CTGCTGCCCG GCTCCTACGG ACTGCCCTTC 60

TACAACGGCT TCTACTACTC CAACAGCGCC AACGACCAGA ACCTAGGCAA CGGTCATGGC 120

AAAGACCTCC TTAATGGAGT GAAGCTGGTG GTGGAGACAC CCGAGGAGAC CCTGTTCACC 180

CGCATCCTAA CTGTGGGCCC CCAGAGCCTG GGGTCCGAAG CTTTGGCTTC CCCGACCCGC 240

AGAGCCGCTT GTACGGTGTT TACTGCTACC GCCAGCACTA GGACCTGGGG CCCTCCCCTG 300

CCGCATTCCC TCACTGGCTG TGTATTTATT GAGTGGTTCG TTTTCCCTTG TGGGTTGGAG 360

CCATTT 366

Sequence length:

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP10368

Sequence description

ATGGAGAAAA TTCCAGTGTC AGCATTCTTG CTCCTTGTGG CCCTCTCCTA CACTCTGGCC 60

AGAGATACCA CAGTCAAACC TGGAGCCAAA AAGGACACAA AGGACTCTCG ACCCAAACTG 120

CCCCAGACCC TCTCCAGAGG TTGGGGTGAC CAACTCATCT GGACTCAGAC ATATGAAGAA 180

GCTCTATATA AATCCAAGAC AAGCAACAAA CCCTTGATGA TTATTCATCA CTTGGATGAG 240

TGCCCACACA GTCAAGCTTT AAAGAAAGTG TTTGCTGAAA ATAAAGAAAT CCAGAAATTG 300

GCAGAGCAGT TTGTCCTCCT CAATCTGGTT TATGAAACAA CTGACAAACA CCTTTCTCCT 360

GATGGCCAGT ATGTCCCCAG GATTATGTTT GTTGACCCAT CTCTGACAGT TAGAGCCGAT 420

ATCACTGGAA GATATTCAAA CCGTCTCTAT GCTTACGAAC CTGCAGATAC AGCTCTGTTG 480

CTTGACAACA TGAAGAAAGC TCTCAAGTTG CTGAAGACTG AATTG 525

Sequence No.: 19

Sequence length: 1296

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Clone name: HP00658

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 56.. 520

Characterization method: E

Sequence description

```
CCTGCAGAGG ATCAAGACAG CACGTGGACC TCGCACAGCC TCTCCCACAG GTACC ATG      58
                                                              Met
                                                               1

AAG GTC TCC GCG GCA GCC CTC GCT GTC ATC CTC ATT GCT ACT GCC CTC      106
Lys Val Ser Ala Ala Ala Leu Ala Val Ile Leu Ile Ala Thr Ala Leu
                5                  10                  15

TGC GCT CCT GCA TCT GCC TCC CCA TAT TCC TCG GAC ACC ACA CCC TGC      154
Cys Ala Pro Ala Ser Ala Ser Pro Tyr Ser Ser Asp Thr Thr Pro Cys
            20                  25                  30

TGC TTT GCC TAC ATT GCC CGC CCA CTG CCC CGT GCC CAC ATC AAG GAG      202
Cys Phe Ala Tyr Ile Ala Arg Pro Leu Pro Arg Ala His Ile Lys Glu
        35                  40                  45

TAT TTC TAC ACC AGT GGC AAG TGC TCC AAC CCA GCA GTC GTC CAC AGG      250
Tyr Phe Tyr Thr Ser Gly Lys Cys Ser Asn Pro Ala Val Val His Arg
    50                  55                  60                  65

TCA AGG ATG CCA AAG AGA GAG GGA CAG CAA GTC TGG CAG GAT TTC CTG      298
Ser Arg Met Pro Lys Arg Glu Gly Gln Gln Val Trp Gln Asp Phe Leu
                70                  75                  80

TAT GAC TCC CGG CTG AAC AAG GGC AAG CTT TGT CAC CCG AAA GAA CCG      346
Tyr Asp Ser Arg Leu Asn Lys Gly Lys Leu Cys His Pro Lys Glu Pro
            85                  90                  95

[illegible]
            100                 105                 110
```

CTC TTT GGA GAT GAG CTA GGA TGG AGA GTC CTT GAA CCT GAA CTT ACA 442
Leu Phe Gly Asp Glu Leu Gly Trp Arg Val Leu Glu Pro Glu Leu Thr
115 120 125

CAA ATT TGC CTG TTT CTG CTT GCT CTT GTC CTA GCT TGG GAG GCT TCC 490
Gln Ile Cys Leu Phe Leu Leu Ala Leu Val Leu Ala Trp Glu Ala Ser
130 135 140 145

CCT CAC TAT CCT ACC CCA CCC GCT CCT TGAAGGGCCC AGA 530
Pro His Tyr Pro Thr Pro Pro Ala Pro
150

TTCTACCACA CAGCAGCAGT TACAAAAACC TTCCCCAGGC TGGACGTGGT GGCTCACGCC 590

TGTAATCCCA GCACTTTGGG AGGCCAAGGT GGGTGGATCA CTTGAGGTCA GGAGTTCGAG 650

ACCAGCCTGG CCAACATGAT GAAACCCCAT CTCTACTAAA AATACAAAAA ATTAGCCGGG 710

CGTGGTAGCG GGCGCCTGTA GTCCCAGCTA CTCGGGAGGC TGAGGCAGGA GAATGGCGTG 770

AACCCGGGAG GCGGAGCTTG CAGTGAGCCG AGATCGCGCC ACTGCACTCC AGCCTGGGCG 830

ACAGAGCGAG ACTCCGTCTC AAAAAAAAAA AAAAAAAAAA AAATACAAAA ATTAGCCGGG 890

CGTGGTGGCC CACGCCTGTA ATCCCAGCTA CTCGGGAGGC TAAGGCAGGA AAATTGTTTG 950

AACCCAGGAG GTGGAGGCTG CAGTGAGCTG AGATTGTGCC ACTTCACTCC AGCCTGGGTG 1010

ACAAAGTGAG ACTCCGTCAC AACAACAACA ACAAAAAGCT TCCCCAACTA AAGCCTAGAA 1070

GAGCTTCTGA GGCGCTGCTT TGTCAAAAGG AAGTCTCTAG GTTCTGAGCT CTGGCTTTGC 1130

CTTGGCTTTG CCAGGGCTCT GTGACCAGGA AGGAAGTCAG CATGCCTCTA GAGGCAAGGA 1190

GGGGAGGAAC GCTGCACTCT TAAGCTTCCG CCGTCTCAAC CCCTCACAGG AGCTTACTGG 1250

CAAACATGAA AAATCGGCTT ACCATTAAAG TTCTCAATGC AACCAT 1296

Sequence No.: 20

Sequence length: 3311

Sequence type: Nucleic acid

[illegible]

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP00714

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 57.. 1004

Characterization method: E

Sequence description

```
GAGCGGCGGC CACGGCATCC TGTGCTGTGG GGGCTACGAG GAAAGATCTA ATTATC ATG      59
                                                                Met
                                                                 1

GAC CTG CGA CAG TTT CTT ATG TGC CTG TCC CTG TGC ACA GCC TTT GCC      107
Asp Leu Arg Gln Phe Leu Met Cys Leu Ser Leu Cys Thr Ala Phe Ala
                5                  10                  15

TTG AGC AAA CCC ACA GAA AAG AAG GAC CGT GTA CAT CAT GAG CCT CAG      155
Leu Ser Lys Pro Thr Glu Lys Lys Asp Arg Val His His Glu Pro Gln
        20                  25                  30

CTC AGT GAC AAG GTT CAC AAT GAT GCT CAG AGT TTT GAT TAT GAC CAT      203
Leu Ser Asp Lys Val His Asn Asp Ala Gln Ser Phe Asp Tyr Asp His
    35                  40                  45

GAT GCC TTC TTG GGT GCT GAA GAA GCA AAG ACC TTT GAT CAG CTG ACA      251
Asp Ala Phe Leu Gly Ala Glu Glu Ala Lys Thr Phe Asp Gln Leu Thr
50                  55                  60                  65

CCA GAA GAG AGC AAG GAA AGG CTT GGA AAG ATT GTA AGT AAA ATA GAT      299


GGC GAC AAG GAC GGG TTT GTC ACT GTG GAT GAG CTC AAA GAC TGG ATT      347
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Gly Asp Lys Asp Gly Phe Val Thr Val Asp Glu Leu Lys Asp Trp Ile
85 90 95

AAA TTT GCA CAA AAG CGC TGG ATT TAC GAG GAT GTA GAG CGA CAG TGG 395
Lys Phe Ala Gln Lys Arg Trp Ile Tyr Glu Asp Val Glu Arg Gln Trp
100 105 110

AAG GGG CAT GAC CTC AAT GAG GAC GGC CTC GTT TCC TGG GAG GAG TAT 443
Lys Gly His Asp Leu Asn Glu Asp Gly Leu Val Ser Trp Glu Glu Tyr
115 120 125

AAA AAT GCC ACC TAC GGC TAC GTT TTA GAT GAT CCA GAT CCT GAT GAT 491
Lys Asn Ala Thr Tyr Gly Tyr Val Leu Asp Asp Pro Asp Pro Asp Asp
130 135 140 145

GGA TTT AAC TAT AAA CAG ATG ATG GTT AGA GAT GAG CGG AGG TTT AAA 539
Gly Phe Asn Tyr Lys Gln Met Met Val Arg Asp Glu Arg Arg Phe Lys
150 155 160

ATG GCA GAC AAG GAT GGA GAC CTC ATT GCC ACC AAG GAG GAG TTC ACA 587
Met Ala Asp Lys Asp Gly Asp Leu Ile Ala Thr Lys Glu Glu Phe Thr
165 170 175

GCT TTC CTG CAC CCT GAG GAG TAT GAC TAC ATG AAA GAT ATA GTA GTA 635
Ala Phe Leu His Pro Glu Glu Tyr Asp Tyr Met Lys Asp Ile Val Val
180 185 190

CAG GAA ACA ATG GAA GAT ATA GAT AAG AAT GCT GAT GGT TTC ATT GAT 683
Gln Glu Thr Met Glu Asp Ile Asp Lys Asn Ala Asp Gly Phe Ile Asp
195 200 205

CTA GAA GAG TAT ATT GGT GAC ATG TAC AGC CAT GAT GGG AAT ACT GAT 731
Leu Glu Glu Tyr Ile Gly Asp Met Tyr Ser His Asp Gly Asn Thr Asp
210 215 220 225

[illegible]
230 235 240

GAT AAG AAC CGT GAT GGG AAG ATG GAC AAG GAA GAG ACC AAA GAC TGG 827
Asp Lys Asn Arg Asp Gly Lys Met Asp Lys Glu Glu Thr Lys Asp Trp
245 250 255

ATC CTT CCC TCA GAC TAT GAT CAT GCA GAG GCA GAA GCC AGG CAC CTG 875
Ile Leu Pro Ser Asp Tyr Asp His Ala Glu Ala Glu Ala Arg His Leu
260 265 270

GTC TAT GAA TCA GAC CAA AAC AAG GAT GGC AAG CTT ACC AAG GAG GAG 923
Val Tyr Glu Ser Asp Gln Asn Lys Asp Gly Lys Leu Thr Lys Glu Glu
275 280 285

ATC GTT GAC AAG TAT GAC TTA TTT GTT GGC AGC CAG GCC ACA GAT TTT 971
Ile Val Asp Lys Tyr Asp Leu Phe Val Gly Ser Gln Ala Thr Asp Phe
290 295 300 305

GGG GAG GCC TTA GTA CGG CAT GAT GAG TTC TGAGCTACGG AGGAACCCT 1020
Gly Glu Ala Leu Val Arg His Asp Glu Phe
310 315

CATTTCCTCA AAAGTAATTT ATTTTTACAG CTTCTGGTTT CACATGAAAT TGTTTGCGCT 1080

ACTGAGACTG TTACTACAAA CTTTTTAAGA CATGAAAAGG CGTAATGAAA ACCATCCCGT 1140

CCCCATTCCT CCTCCTCTCT GAGGGACTGG AGGGAAGCCG TGCTTCTGAG GAACAACTCT 1200

AATTAGTACA CTTGTGTTTG TAGATTTACA CTTTGTATTA TGTATTAACA TGGCGTGTTT 1260

ATTTTTGTAT TTTTCTCTGG TTGGGAGTAT GATATGAAGG ATCAAGATCC TCAACTCACA 1320

CATGTAGACA AACATTAGCT CTTTACTCTT TCTCAACCCC TTTTATGATT TTAATAATTC 1380

TCACTTAACT AATTTTGTAA GCCTGAGATC AATAAGAAAT GTTCAGGAGA GAGGAAAGAA 1440

AAAAAATATA TGCTCCACAA TTTATATTTA GAGAGAGAAC ACTTAGTCTT GCCTGTCAAA 1500

AAGTCCAACA TTTCATAGGT AGTAGGGGCC ACATATTACA TTCAGTTGCT ATAGGTCCAG 1560

CAACTGAACC TGCCATTACC TGGGCAAGGA AAGATCCCTT TGCTCTAGGA AAGCTTGGCC 1620

CAAATTGATT TTCTTCTTTT TCCCCCTGTA GGACTGACTG TTGGCTAATT TTGTCAAGCA 1680

TTGTTTGCA GAGCTATAGA TAGAAACAGC TGGAAAACTA AAGGAAAAA ACAAGTGTTT

TCGGGGCATA CATTTTTTTT CTGGGTGTGC ATCTGTTGAA ATGCTCAAGA CTTAATTATT 1860

TGCCTTTTGA AATCACTGTA AATGCCCCCA TCCGGTTCCT CTTCTTCCCA GGTGTGCCAA 1920

GGAATTAATC TTGGTTTCAC TACAATTAAA ATTCACTCCT TTCCAATCAT GTCATTGAAA 1980

GTGCCTTTAA CGAAAGAAAT GGTCACTGAA TGGGAATTCT CTTAAGAAAC CCTGAGATTA 2040

AAAAAAGACT ATTTGGATAA CTTATAGGAA AGCCTAGAAC CTCCCAGTAG AGTGGGGATT 2100

TTTTTCTTCT TCCCTTTCTC TTTTGGACAA TAGTTAAATT AGCAGTATTA GTTATGAGTT 2160

TGGTTGCAGT GTTCTTATCT TGTGGGCTGA TTTCCAAAAA CCACATGCTG CTGAATTTAC 2220

CAGGGATCCT CATACCTCAC AATGCAAACC ACTTACTACC AGGCCTTTTT CTGTGTCCAC 2280

TGGAGAGCTT GAGCTCACAC TCAAAGATCA GAGGACCTAC AGAGAGGGCT CTTTGGTTTG 2340

AGGACCATGG CTTACCTTTC CTGCCTTTGA CCCATCACAC CCCATTTCCT CCTCTTTCCC 2400

TCTCCCCGCT GCCAAAAAAA AAAAAAAAAG GAAACGTTTA TCATGAATCA ACAGGGTTTC 2460

AGTCCTTATC AAAGAGAGAT GTGGAAAGAG CTAAAGAAAC CACCCTTTGT TCCCAACTCC 2520

ACTTTACCCA TATTTTATGC AACACAAACA CTGTCCTTTT GGGTCCCTTT CTTACAGATG 2580

GACCTCTTGA GAAGAATTAT CGTATTCCAC GTTTTTAGCC CTCAGGTTAC CAAGATAAAT 2640

ATATGTATAT ATAACCTTTA TTATTGCTAT ATCTTTGTGG ATAATACATT CAGGTGGTGC 2700

TGGGTGATTT ATTATAATCT GAACCTAGGT ATATCCTTTG GTCTTCCACA GTCATGTTGA 2760

GGTGGGCTCC CTGGTATGGT AAAAAGCCAG GTATAATGTA ACTTCACCCC AGCCTTTGTA 2820

CTAAGCTCTT GATAGTGGAT ATACTCTTTT AAGTTTAGCC CCAATATAGG GTAATGGAAA 2880

TTTCCTGCCC TCTGGGTTCC CCATTTTTAC TATTAAGAAG ACCAGTGATA ATTTAATAAT 2940

GCCACCAACT CTGGCTTAGT TAAGTGAGAG TGTGAACTGT GTGGCAAGAG AGCCTCACAC 3000

CTCACTAGGT GCAGAGAGCC CAGGCCTTAT GTTAAAATCA TGCACTTGAA AAGCAAACCT 3060

TAATCTGCAA AGACAGCAGC AAGCATTATA CGGTCATCTT GAATGATCCC TTTGAAATTT 3120

TTTTTTTGTT TGTTTGTTTA AATCAAGCCT GAGGCTGGTG AACAGTAGCT ACACACCCAT 3180

ATTGTGTGTT CTGTGAATGC TAGCTTTCTT GAATTTGGAT ATTGGTTATT TTTTATAGAG 3240

TGTAAACCAA GTTTTATATT CTGCAATGCG AACAGGTACC TATCTGTTTC TAAATAAAAC 3300

TGTTTACATT C 3311

Sequence length

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP00876

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 147.. 623

Characterization method: E

Sequence description

```
ACTGGAGACA CTGAAGAAGG CAGGGGCCCT TAGAGTCTTG GTTGCCAAAC AGATTTGCAG      60
ATCAAGGAGA ACCCAGGAGT TTCAAAGAAG CGCTAGTAAG GTCTCTGAGA TCCTTGCACT     120
AGCTACATCC TCAGGGTAGG AGGAAG ATG GCT TCC AGA AGC ATG CGG CTG CTC       173
                             Met Ala Ser Arg Ser Met Arg Leu Leu
                                                 1               5

CTA TTG CTG AGC TGC CTG GCC AAA ACA GGA GTC CTG GGT GAT ATC ATC       221
Leu Leu Leu Ser Cys Leu Ala Lys Thr Gly Val Leu Gly Asp Ile Ile
 10                  15                  20                  25

ATG AGA CCC AGC TGT GCT CCT GGA TGG TTT TAC CAC AAG TCC AAT TGC       269
Met Arg Pro Ser Cys Ala Pro Gly Trp Phe Tyr His Lys Ser Asn Cys
                 30                  35                  40

TAT GGT TAC TTC AGG AAG CTG AGG AAC TGG TCT GAT GCC GAG CTC GAG       317
Tyr Gly Tyr Phe Arg Lys Leu Arg Asn Trp Ser Asp Ala Glu Leu Glu
             45                  50                  55

                                                                     [illegible]
                                                                     [illegible]
         60                  65                  70
```

```
AAG GAA GCC AGC ACC ATA GCA GAG TAC ATA AGT GGC TAT CAG AGA AGC      413
Lys Glu Ala Ser Thr Ile Ala Glu Tyr Ile Ser Gly Tyr Gln Arg Ser
     75                  80                  85

CAG CCG ATA TGG ATT GGC CTG CAC GAC CCA CAG AAG AGG CAG CAG TGG      461
Gln Pro Ile Trp Ile Gly Leu His Asp Pro Gln Lys Arg Gln Gln Trp
 90                  95                 100                 105

CAG TGG ATT GAT GGG GCC ATG TAT CTG TAC AGA TCC TGG TCT GGC AAG      509
Gln Trp Ile Asp Gly Ala Met Tyr Leu Tyr Arg Ser Trp Ser Gly Lys
                110                 115                 120

TCC ATG GGT GGG AAC AAG CAC TGT GCT GAG ATG AGC TCC AAT AAC AAC      557
Ser Met Gly Gly Asn Lys His Cys Ala Glu Met Ser Ser Asn Asn Asn
            125                 130                 135

TTT TTA ACT TGG AGC AGC AAC GAA TGC AAC AAG CGC CAA CAC TTC CTG      605
Phe Leu Thr Trp Ser Ser Asn Glu Cys Asn Lys Arg Gln His Phe Leu
        140                 145                 150

TGC AAG TAC CGA CCA TAGAGCAAGA ATCAAGATTC TGCTAACTCC                 650
Cys Lys Tyr Arg Pro
    155

TGCACAGCCC CGTCCTCTTC CTTTCTGCTA GCCTGGCTAA ATCTGCTCAT TATTTCAGAG    710

GGGAAACCTA GCAAACTAAG AGTGATAAGG GCCCTACTAC ACTGGCTTTT TTAGGCTTAG    770

AGACAGAAAC TTTAGCATTG GCCCAGTAGT GGCTTCTAGC TCTAAATGTT TGCCCCGCCA    830

TCCCTTTCCA CAGTATCCTT CTTCCCTCCT CCCCTGTCTC TGGCTGTCTC GAGCAGTCTA    890

GAAGAGTGCA TCTCCAGCCT ATGAAACAGC TGGGTCTTTG GCCATAAGAA GTAAAGATTT    950

GAAGACAGAA GGAAGAAACT CAGGAGTAAG CTTCTAGCCC CCTTCAGCTT CTACACCCTT   1010

CTGCCCTCTC TCCATTGCCT GCACCCCACC CCAGCCACTC AACTCCTGCT TGTTTTTCCT   1070

TTGGCCATGG GAAGGTTTAC CAGTAGAATC CTTGCTAGGT TGATGTGGGC CATACATTCC   1130
```

Sequence No.: 22

Sequence length: 1749

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Liver

Clone name: HP01134

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 117.. 1247

Characterization method: E

Sequence description

```
AATCACAGCA GTNCCGACGT CGTGGGTGTT TGGTGTGAGG CTGCGAGCCG CCGCCGCCAC      60
CACTGCCACC ACGGTCGCCT GCCACAGGTG TCTGCAATTG AACTCCAAGG TGCAGA ATG      119
                                                                 Met
                                                                   1
GTT TGG AAA GTA GCT GTA TTC CTC AGT GTG GCC CTG GGC ATT GGT GCC         167
Val Trp Lys Val Ala Val Phe Leu Ser Val Ala Leu Gly Ile Gly Ala
  5                  10                  15
GTT CCT ATA GAT GAT CCT GAA GAT GGA GGC AAG CAC TGG GTG GTG ATC         215
Val Pro Ile Asp Asp Pro Glu Asp Gly Gly Lys His Trp Val Val Ile
            20                  25                  30
GTG GCA GGT TCA AAT GGC TGG TAT AAT TAT AGG CAC CAG GCA GAC GCG         263
Val Ala Gly Ser Asn Gly Trp Tyr Asn Tyr Arg His Gln Ala Asp Ala
```

```
Cys His Ala Tyr Gln Ile Ile His Arg Asn Gly Ile Pro Asp Glu Gln
```

50 55 60 65

ATC GTT GTG ATG ATG TAC GAT GAC ATT GCT TAC TCT GAA GAC AAT CCC 359
Ile Val Val Met Met Tyr Asp Asp Ile Ala Tyr Ser Glu Asp Asn Pro

70 75 80

ACT CCA GGA ATT GTG ATC AAC AGG CCC AAT GGC ACA GAT GTC TAT CAG 407
Thr Pro Gly Ile Val Ile Asn Arg Pro Asn Gly Thr Asp Val Tyr Gln

85 90 95

GGA GTC CCG AAG GAC TAC ACT GGA GAG GAT GTT ACC CCA CAA AAT TTC 455
Gly Val Pro Lys Asp Tyr Thr Gly Glu Asp Val Thr Pro Gln Asn Phe

100 105 110

CTT GCT GTG TTG AGA GGC GAT GCA GAA GCA GTG AAG GGC ATA GGA TCC 503
Leu Ala Val Leu Arg Gly Asp Ala Glu Ala Val Lys Gly Ile Gly Ser

115 120 125

GGC AAA GTC CTG AAG AGT GGC CCC CAG GAT CAC GTG TTC ATT TAC TTC 551
Gly Lys Val Leu Lys Ser Gly Pro Gln Asp His Val Phe Ile Tyr Phe

130 135 140 145

ACT GAC CAT GGA TCT ACT GGA ATA CTG GTT TTT CCC AAT GAA GAT CTT 599
Thr Asp His Gly Ser Thr Gly Ile Leu Val Phe Pro Asn Glu Asp Leu

150 155 160

CAT GTA AAG GAC CTG AAT GAG ACC ATC CAT TAC ATG TAC AAA CAC AAA 647
His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His Lys

165 170 175

ATG TAC CGA AAG ATG GTG TTC TAC ATT GAA GCC TGT GAG TCT GGG TCC 695
Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly Ser

180 185 190

ATG ATG AAC CAC CTG CCG GAT AAC ATC AAT GTT TAT GCA ACT ACT GCT 743

GCC AAC CCC AGA GAG TCG TCC TAC GCC TGT TAC TAT GAT GAG AAG AGG 791

Ala Asn Pro Arg Glu Ser Ser Tyr Ala Cys Tyr Tyr Asp Glu Lys Arg

210 215 220 225

TCC ACG TAC CTG GGG GAC TGG TAC AGC GTC AAC TGG ATG GAA GAC TCG 839

Ser Thr Tyr Leu Gly Asp Trp Tyr Ser Val Asn Trp Met Glu Asp Ser

230 235 240

GAC GTG GAA GAT CTG ACT AAA GAG ACC CTG CAC AAG CAG TAC CAC CTG 887

Asp Val Glu Asp Leu Thr Lys Glu Thr Leu His Lys Gln Tyr His Leu

245 250 255

GTA AAA TCG CAC ACC AAC ACC AGC CAC GTC ATG CAG TAT GGA AAC AAA 935

Val Lys Ser His Thr Asn Thr Ser His Val Met Gln Tyr Gly Asn Lys

260 265 270

ACA ATC TCC ACC ATG AAA GTG ATG CAG TTT CAG GGT ATG AAA CGC AAA 983

Thr Ile Ser Thr Met Lys Val Met Gln Phe Gln Gly Met Lys Arg Lys

275 280 285

GCC AGT TCT CCC GTC CCC CTA CCT CCA GTC ACA CAC CTT GAC CTC ACC 1031

Ala Ser Ser Pro Val Pro Leu Pro Pro Val Thr His Leu Asp Leu Thr

290 295 300 305

CCC AGC CCT GAT GTG CCT CTC ACC ATC ATG AAA AGG AAA CTG ATG AAC 1079

Pro Ser Pro Asp Val Pro Leu Thr Ile Met Lys Arg Lys Leu Met Asn

310 315 320

ACC AAT GAT CTG GAG GAG TCC AGG CAG CTC ACG GAG GAG ATC CAG CGG 1127

Thr Asn Asp Leu Glu Glu Ser Arg Gln Leu Thr Glu Glu Ile Gln Arg

325 330 335

CAT CTG GAT TAC GAG TAT GCG TTG AGA CAT TTG TAC GTG CTG GTC AAC 1175

His Leu Asp Tyr Glu Tyr Ala Leu Arg His Leu Tyr Val Leu Val Asn

340 345 350

355 360 365

CAC GTG TGC CTT GGT CAC TAC TGAAGAGCTG CCTCCTGGAA GCTTTT 1270

His Val Cys Leu Gly His Tyr

370 375

CCAAGTGTGA GCGCCCCACC GACTGTGTGC TGATCAGAGA CTGGAGAGGT GGAGTGAGAA 1330

GTCTCCGCTG CTCGGGCCCT CCTGGGGAGC CCCCGCTCCA GGGCTCGCTC CAGGACCTTC 1390

TTCACAAGAT GACTTGCTCG CTGTTACCTG CTTCCCCAGT CTTTTCTGAA AAACTACAAA 1450

TTAGGGTGGG AAAAGCTCTG TATTGAGAAG GGTCATATTT GCTTTCTAGG AGGTTTGTTG 1510

TTTTGCCTGT TAGTTTTGAG GAGCAGGAAG CTCATGGGGG CTTCTGTAGC CCCTCTCAAA 1570

AGGAGTCTTT ATTCTGAGAA TTTGAAGCTG AAACCTCTTT AAATCTTCAG AATGATTTTA 1630

TTGAAGAGGG CCGCAAGCCC CAAATGGAAA ACTGTTTTTA GAAAATATGA TGATTTTTGA 1690

TTGCTTTTGT ATTTAATTCT GCAGGTGTTC AAGTCTTAAA AAATAAAGAT TTATAACAG 1749

Sequence No.: 23

Sequence length: 988

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10029

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 9.. 530

Sequence description:

AGTCCAAC ATG GCG GCG CCC AGC GGA GGG TGG AAC GGC GTC CGC GCG AGC 50

Met Ala Ala Pro Ser Gly Gly Trp Asn Gly Val Arg Ala Ser

1 5 10

TTG TGG GCC GCG CTG CTC CTA GGG GCC GTG GCG CTG AGG CCG GCG GAG 98

Leu Trp Ala Ala Leu Leu Leu Gly Ala Val Ala Leu Arg Pro Ala Glu

15 20 25 30

GCG GTG TCC GAG CCC ACG ACC GTG GCG TTT GAC GTG CGG CCC GGC GGC 146

Ala Val Ser Glu Pro Thr Thr Val Ala Phe Asp Val Arg Pro Gly Gly

35 40 45

GTC GTG CAT TCC TTC TCC CAT AAC GTG GGC CCG GGG GAC AAA TAT ACG 194

Val Val His Ser Phe Ser His Asn Val Gly Pro Gly Asp Lys Tyr Thr

50 55 60

TGT ATG TTC ACT TAC GCC TCT CAA GGA GGG ACC AAT GAG CAA TGG CAG 242

Cys Met Phe Thr Tyr Ala Ser Gln Gly Gly Thr Asn Glu Gln Trp Gln

65 70 75

ATG AGT CTG GGG ACC AGC GAA GAC CAC CAG CAC TTC ACC TGC ACC ATC 290

Met Ser Leu Gly Thr Ser Glu Asp His Gln His Phe Thr Cys Thr Ile

80 85 90

TGG AGG CCC CAG GGG AAG TCC TAT CTG TAC TTC ACA CAG TTC AAG GCA 338

Trp Arg Pro Gln Gly Lys Ser Tyr Leu Tyr Phe Thr Gln Phe Lys Ala

95 100 105 110

GAG GTG CGG GGC GCT GAG ATT GAG TAC GCC ATG GCC TAC TCT AAA GCC 386

Glu Val Arg Gly Ala Glu Ile Glu Tyr Ala Met Ala Tyr Ser Lys Ala

115 120 125

GCA TTT GAA AGG GAA AGT GAT GTC CCT CTG AAA ACT GAG GAA TTT GAA 434

Ala Phe Glu Arg Glu Ser Asp Val Pro Leu Lys Thr Glu Glu Phe Glu

130 135 140

145 150 155

CTG TCC AAG CTG GTG ATT GTG GCC AAG GCA TCG CGC ACT GAG CTG 527

Leu Ser Lys Leu Val Ile Val Ala Lys Ala Ser Arg Thr Glu Leu

160 165 170

TGA CCAGCAGCCC TGTTGCGGGT GGCACCTTCT CATCTCCGGT GAAGCTGAAG 580

GGGCCTGTGG CCCTGAAAGG GCCAGCACAT CACTGGTTTT CTAGGAGGGA CTCTTAAGTT 640

TTCTACCTGG GCTGACGTTG CCTTGTCCGG AGGGGCTTGC AGGGTGGCTG AAGCCCTGGG 700

GCAGAGAACA GAGGGTCCAG GGCCCTCCTG GCTCCCAACA GCTTCTCAGT TCCCACTTCC 760

TGCTGAGCTC TTCTGGACTC AGGATCGCAG ATCCGGGGCA CAAAGAGGGT GGGGAACATG 820

GGGGCTATGC TGGGGAAAGC AGCCATGCTC CCCCCGACCT CCAGCCGAGC ATCCTTCATG 880

AGCCTGCAGA ACTGCTTTCC TATGTTTACC CAGGGGACCT CCTTTCAGAT GAACTGGGAA 940

GAGATGAAAT GTTTTTTCAT ATTTAAATAA ATAAGAACAT TAAAAAGC 988

Sequence No.: 24

Sequence length: 390

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Epidermoid carcinoma

Cell line: KB

Clone name: HP10189

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 102.. 323

Sequence description:

AATCAGCTTC AGCAATGGAG CGTGCAAAAC ACCAGTGAGC TTCTGTCTTG CTGGAGGGTC 60

GGCTTTGGGC GGAACTGGCT TTGTTGACCG GGAGAAACGA G ATG GGG GTG AAG CTG 116

Met Gly Val Lys Leu

1 5

GAG ATA TTT CGG ATG ATA ATC TAC CTC ACT TTC CCT GTG GCT ATG TTC 164

Glu Ile Phe Arg Met Ile Ile Tyr Leu Thr Phe Pro Val Ala Met Phe

10 15 20

TGG GTT TCC AAT CAG GCC GAG TGG TTT GAG GAC GAT GTC ATA CAG CGC 212

Trp Val Ser Asn Gln Ala Glu Trp Phe Glu Asp Asp Val Ile Gln Arg

25 30 35

AAG AGG GAG CTG TGG CCA CCT GAG AAG CTT CAA GAG ATA GAG GAA TTC 260

Lys Arg Glu Leu Trp Pro Pro Glu Lys Leu Gln Glu Ile Glu Glu Phe

40 45 50

AAA GAG AGG TTA CGG AAG CGG CGG GAG GAG AAG CTC CTT CGC GAC GCC 308

Lys Glu Arg Leu Arg Lys Arg Arg Glu Glu Lys Leu Leu Arg Asp Ala

55 60 65

CAG CAG AAC TCC TGAGGCCTCC AAGTGGGAGT CCTAGCCCCT 350

Gln Gln Asn Ser

70

CCCCTGATGA AATATACATA TACTCAGTTC CTTGTTATTC 390

Sequence No.: 25

Sequence length: 4667

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

[illegible]

Cell kind: Lymphoma

Cell line: U937

Clone name: HP10269

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 754.. 4272

Characterization method: E

Sequence description

CATTTAGTTA CTCTGCTCAT TTCTCTTAAG CTTTCCTTGG ATGAGTTGAG CTTTGAATCC 60

TTCCTGATGA ACCTTGCCTT TTAAGGATCC TCCAAATGCC CCAAGAAGCT GGGATTTTTC 120

ATTTTTTTTT TCACTGGGGA GGGGAATGGT GCTTTCCAGG GTCCTGGATG TTTGAGTCTT 180

CTCACCTTCC AGCCCGGTGA TATGTCTGGA GCTTTAACTC TCTATATAAG CCCTAATCTT 240

TGTGTTCTCT GCCTGATCTT CTGTCTGGGG TGGTCCAGGT CACAAGAAGA AGCTGACCCC 300

TGCTGGCTTT GGGAAAATGC TGAGTTCATT GCCTGGCACA AATGCAAGGG CCCTTCCCCA 360

CCCTGTGAAT TCTGGTCTCT GATGATCACT TACATGTGCC TTGTGCTTTC TGTTTGAGGG 420

GCCCCTTGCA GCCCCCACAG GCAGGTGGGC ATTGTGGAGC TCACTACAAG AACTCTGGGA 480

CCGACCGACC AACCCACTTG CCCAGTCCCG TCCTGGGAGG TGGGGGTGCA GTGACGACAG 540

ATGGGTGTGA CGGCTGCCAG ATTCCTGAGA CCCGCCCTGC GGTGGGGCTA CACCCAGCCA 600

GGGAGTCTCC AGAGGTGAGG CTGTTGTTTA AAAACCTGGA GCCGGGAGGG GAGACCCCCA 660

CATTCAAGAG GAGCTTTCAG GCGATCTGGA GAAAGAACGG CAGAACACAC AGCAAGGAAA 720

GGTCCTTTCT GGGGATCACC CCATTGGCTG AAG ATG AGA CCA TTC TTC CTC TTG 774

Met Arg Pro Phe Phe Leu Leu

1 5

TGT TTT GCC CTG CCT GGC CTC CTG CAT GCC CAA CAA GCC TGC TCC CGT 822

Cys Phe Ala Leu Pro Gly Leu Leu His Ala Gln Gln Ala Cys Ser Arg

10 15 20

GGG GCC TGC TAT CCA CCT GTT GGG GAC CTG CTT GTT GGG AGG ACC CGG 870

TTT CTC CGA GCT TCA TCT ACC TGT GGA CTG ACC AAG CCT GAG ACC TAC 918

```
Phe Leu Arg Ala Ser Ser Thr Cys Gly Leu Thr Lys Pro Glu Thr Tyr
 40                  45                  50                  55
TGC ACC CAG TAT GGC GAG TGG CAG ATG AAA TGC TGC AAG TGT GAC TCC      966
Cys Thr Gln Tyr Gly Glu Trp Gln Met Lys Cys Cys Lys Cys Asp Ser
                    60                  65                  70
AGG CAG CCT CAC AAC TAC TAC AGT CAC CGA GTA GAG AAT GTG GCT TCA     1014
Arg Gln Pro His Asn Tyr Tyr Ser His Arg Val Glu Asn Val Ala Ser
                75                  80                  85
TCC TCC GGC CCC ATG CGC TGG TGG CAG TCC CAG AAT GAT GTG AAC CCT     1062
Ser Ser Gly Pro Met Arg Trp Trp Gln Ser Gln Asn Asp Val Asn Pro
            90                  95                  100
GTC TCT CTG CAG CTG GAC CTG GAC AGG AGA TTC CAG CTT CAA GAA GTC     1110
Val Ser Leu Gln Leu Asp Leu Asp Arg Arg Phe Gln Leu Gln Glu Val
        105                 110                 115
ATG ATG GAG TTC CAG GGG CCC ATG CCT GCC GGC ATG CTG ATT GAG CGC     1158
Met Met Glu Phe Gln Gly Pro Met Pro Ala Gly Met Leu Ile Glu Arg
    120                 125                 130                 135
TCC TCA GAC TTC GGT AAG ACC TGG CGA GTG TAC CAG TAC CTG GCT GCC     1206
Ser Ser Asp Phe Gly Lys Thr Trp Arg Val Tyr Gln Tyr Leu Ala Ala
                140                 145                 150
GAC TGC ACC TCC ACC TTC CCT CGG GTC CGC CAG GGT CGG CCT CAG AGC     1254
Asp Cys Thr Ser Thr Phe Pro Arg Val Arg Gln Gly Arg Pro Gln Ser
            155                 160                 165
TGG CAG GAT GTT CGG TGC CAG TCC CTG CCT CAG AGG CCT AAT GCA CGC     1302
Trp Gln Asp Val Arg Cys Gln Ser Leu Pro Gln Arg Pro Asn Ala Arg
        170                 175                 180

    185                 190                 195
```

ATT CCA GCA ACT CAA AGT CAA AAA ATT CAA GAG GTG GGG GAG ATC ACA 1398
Ile Pro Ala Thr Gln Ser Gln Lys Ile Gln Glu Val Gly Glu Ile Thr
200 205 210 215

AAC TTG AGA GTC AAT TTC ACC AGG CTG GCC CCT GTG CCC CAA AGG GGC 1446
Asn Leu Arg Val Asn Phe Thr Arg Leu Ala Pro Val Pro Gln Arg Gly
220 225 230

TAC CAC CCT CCC AGC GCC TAC TAT GCT GTG TCC CAG CTC CGT CTG CAG 1494
Tyr His Pro Pro Ser Ala Tyr Tyr Ala Val Ser Gln Leu Arg Leu Gln
235 240 245

GGG AGC TGC TTC TGT CAC GGC CAT GCT GAT CGC TGC GCA CCC AAG CCT 1542
Gly Ser Cys Phe Cys His Gly His Ala Asp Arg Cys Ala Pro Lys Pro
250 255 260

GGG GCC TCT GCA GGC CCC TCC ACC GCT GTG CAG GTC CAC GAT GTC TGT 1590
Gly Ala Ser Ala Gly Pro Ser Thr Ala Val Gln Val His Asp Val Cys
265 270 275

GTC TGC CAG CAC AAC ACT GCC GGC CCA AAT TGT GAG CGC TGT GCA CCC 1638
Val Cys Gln His Asn Thr Ala Gly Pro Asn Cys Glu Arg Cys Ala Pro
280 285 290 295

TTC TAC AAC AAC CGG CCC TGG AGA CCG GCG GAG GGC CAG GAC GCC CAT 1686
Phe Tyr Asn Asn Arg Pro Trp Arg Pro Ala Glu Gly Gln Asp Ala His
300 305 310

GAA TGC CAA AGG TGC GAC TGC AAT GGG CAC TCA GAG ACA TGT CAC TTT 1734
Glu Cys Gln Arg Cys Asp Cys Asn Gly His Ser Glu Thr Cys His Phe
315 320 325

GAC CCC GCT GTG TTT GCC GCC AGC CAG GGG GCA TAT GGA GGT GTG TGT 1782
Asp Pro Ala Val Phe Ala Ala Ser Gln Gly Ala Tyr Gly Gly Val Cys

Asp Asn Cys Arg Asp His Thr Glu Gly Lys Asn Cys Glu Arg Cys Gln

```
     345                 350                 355
CTG CAC TAT TTC CGG AAC CGG CGC CCG GGA GCT TCC ATT CAG GAG ACC      1878
Leu His Tyr Phe Arg Asn Arg Arg Pro Gly Ala Ser Ile Gln Glu Thr
360                 365                 370                 375
TGC ATC TCC TGC GAG TGT GAT CCG GAT GGG GCA GTG CCA GGG GCT CCC      1926
Cys Ile Ser Cys Glu Cys Asp Pro Asp Gly Ala Val Pro Gly Ala Pro
                380                 385                 390
TGT GAC CCA GTG ACC GGG CAG TGT GTG TGC AAG GAG CAT GTG CAG GGA      1974
Cys Asp Pro Val Thr Gly Gln Cys Val Cys Lys Glu His Val Gln Gly
            395                 400                 405
GAG CGC TGT GAC CTA TGC AAG CCG GGC TTC ACT GGA CTC ACC TAC GCC      2022
Glu Arg Cys Asp Leu Cys Lys Pro Gly Phe Thr Gly Leu Thr Tyr Ala
        410                 415                 420
AAC CCG CAG GGC TGC CAC CGC TGT GAC TGC AAC ATC CTG GGG TCC CGG      2070
Asn Pro Gln Gly Cys His Arg Cys Asp Cys Asn Ile Leu Gly Ser Arg
    425                 430                 435
AGG GAC ATG CCG TGT GAC GAG GAG AGT GGG CGC TGC CTT TGT CTG CCC      2118
Arg Asp Met Pro Cys Asp Glu Glu Ser Gly Arg Cys Leu Cys Leu Pro
440                 445                 450                 455
AAC GTG GTG GGT CCC AAA TGT GAC CAG TGT GCT CCC TAC CAC TGG AAG      2166
Asn Val Val Gly Pro Lys Cys Asp Gln Cys Ala Pro Tyr His Trp Lys
                460                 465                 470
CTG GCC AGT GGC CAG GGC TGT GAA CCG TGT GCC TGC GAC CCG CAC AAC      2214
Leu Ala Ser Gly Gln Gly Cys Glu Pro Cys Ala Cys Asp Pro His Asn
            475                 480                 485
TCC CTC AGC CCA CAG TGC AAC CAG TTC ACA GGG CAG TGC CCC TGT CGG      2262

GAA GGC TTT GGT GGC CTG ATG TGC AGC GCT GCA GCC ATC CGC CAG TGT      2310
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Glu Gly Phe Gly Gly Leu Met Cys Ser Ala Ala Ala Ile Arg Gln Cys
505 510 515

CCA GAC CGG ACC TAT GGA GAC GTG GCC ACA GGA TGC CGA GCC TGT GAC 2358
Pro Asp Arg Thr Tyr Gly Asp Val Ala Thr Gly Cys Arg Ala Cys Asp
520 525 530 535

TGT GAT TTC CGG GGA ACA GAG GGC CCG GGC TGC GAC AAG GCA TCA GGC 2406
Cys Asp Phe Arg Gly Thr Glu Gly Pro Gly Cys Asp Lys Ala Ser Gly
540 545 550

CGC TGC CTC TGC CGC CCT GGC TTG ACC GGG CCC CGC TGT GAC CAG TGC 2454
Arg Cys Leu Cys Arg Pro Gly Leu Thr Gly Pro Arg Cys Asp Gln Cys
555 560 565

CAG CGA GGC TAC TGC AAT CGC TAC CCG GTG TGC GTG GCC TGC CAC CCT 2502
Gln Arg Gly Tyr Cys Asn Arg Tyr Pro Val Cys Val Ala Cys His Pro
570 575 580

TGC TTC CAG ACC TAT GAT GCG GAC CTC CGG GAG CAG GCC CTG CGC TTT 2550
Cys Phe Gln Thr Tyr Asp Ala Asp Leu Arg Glu Gln Ala Leu Arg Phe
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GGT AGA CTC CGC AAT GCC ACC GCC AGC CTG TGG TCA GGG CCT GGG CTG 2598
Gly Arg Leu Arg Asn Ala Thr Ala Ser Leu Trp Ser Gly Pro Gly Leu
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GAG GAC CGT GGC CTG GCC TCC CGG ATC CTA GAT GCA AAG AGT AAG ATT 2646
Glu Asp Arg Gly Leu Ala Ser Arg Ile Leu Asp Ala Lys Ser Lys Ile
620 625 630

GAG CAG ATC CGA GCA GTT CTC AGC AGC CCC GCA GTC ACA GAG CAG GAG 2694
Glu Gln Ile Arg Ala Val Leu Ser Ser Pro Ala Val Thr Glu Gln Glu
635 640 645

650 655 660

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Gly Leu Gln Leu Asp Leu Pro Leu Glu Glu Glu Thr Leu Ser Leu Pro
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AGA GAC CTG GAG AGT CTT GAC AGA AGC TTC AAT GGT CTC CTT ACT ATG      2838
Arg Asp Leu Glu Ser Leu Asp Arg Ser Phe Asn Gly Leu Leu Thr Met
680                 685                 690                 695
TAT CAG AGG AAG AGG GAG CAG TTT GAA AAA ATA AGC AGT GCT GAT CCT      2886
Tyr Gln Arg Lys Arg Glu Gln Phe Glu Lys Ile Ser Ser Ala Asp Pro
                700                 705                 710
TCA GGA GCC TTC CGG ATG CTG AGC ACA GCC TAC GAG CAG TCA GCC CAG      2934
Ser Gly Ala Phe Arg Met Leu Ser Thr Ala Tyr Glu Gln Ser Ala Gln
            715                 720                 725
GCT GCT CAG CAG GTC TCC GAC AGC TCG CGC CTT TTG GAC CAG CTC AGG      2982
Ala Ala Gln Gln Val Ser Asp Ser Ser Arg Leu Leu Asp Gln Leu Arg
        730                 735                 740
GAC AGC CGG AGA GAG GCA GAG AGG CTG GTG CGG CAG GCG GGA GGA GGA      3030
Asp Ser Arg Arg Glu Ala Glu Arg Leu Val Arg Gln Ala Gly Gly Gly
    745                 750                 755
GGA GGC ACC GGC AGC CCC AAG CTT GTG GCC CTG AGG CTG GAG ATG TCT      3078
Gly Gly Thr Gly Ser Pro Lys Leu Val Ala Leu Arg Leu Glu Met Ser
760                 765                 770                 775
TCG TTG CCT GAC CTG ACA CCC ACC TTC AAC AAG CTC TGT GGC AAC TCC      3126
Ser Leu Pro Asp Leu Thr Pro Thr Phe Asn Lys Leu Cys Gly Asn Ser
                780                 785                 790
AGG CAG ATG GCT TGC ACC CCA ATA TCA TGC CCT GGT GAG CTA TGT CCC      3174
Arg Gln Met Ala Cys Thr Pro Ile Ser Cys Pro Gly Glu Leu Cys Pro

[illegible]

Gln Asp Asn Gly Thr Ala Cys Gly Ser Arg Cys Arg Gly Val Leu Pro
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AGG GCC GGT GGG GCC TTC TTG ATG GCG GGG CAG GTG GCT GAG CAG CTG      3270
Arg Ala Gly Gly Ala Phe Leu Met Ala Gly Gln Val Ala Glu Gln Leu
    825                 830                 835
CGG GGC TTC AAT GCC CAG CTC CAG CGG ACC AGG CAG ATG ATT AGG GCA      3318
Arg Gly Phe Asn Ala Gln Leu Gln Arg Thr Arg Gln Met Ile Arg Ala
840                 845                 850                 855
GCC GAG GAA TCT GCC TCA CAG ATT CAA TCC AGT GCC CAG CGC TTG GAG      3366
Ala Glu Glu Ser Ala Ser Gln Ile Gln Ser Ser Ala Gln Arg Leu Glu
                860                 865                 870
ACC CAG GTG AGC GCC AGC CGC TCC CAG ATG GAG GAA GAT GTC AGA CGC      3414
Thr Gln Val Ser Ala Ser Arg Ser Gln Met Glu Glu Asp Val Arg Arg
            875                 880                 885
ACA CGG CTC CTA ATC CAG CAG GTC CGG GAC TTC CTA ACA GAC CCC GAC      3462
Thr Arg Leu Leu Ile Gln Gln Val Arg Asp Phe Leu Thr Asp Pro Asp
        890                 895                 900
ACT GAT GCA GCC ACT ATC CAG GAG GTC AGC GAG GCC GTG CTG GCC CTG      3510
Thr Asp Ala Ala Thr Ile Gln Glu Val Ser Glu Ala Val Leu Ala Leu
    905                 910                 915
TGG CTG CCC ACA GAC TCA GCT ACT GTT CTG CAG AAG ATG AAT GAG ATC      3558
Trp Leu Pro Thr Asp Ser Ala Thr Val Leu Gln Lys Met Asn Glu Ile
920                 925                 930                 935
CAG GCC ATT GCA GCC AGG CTC CCC AAC GTG GAC TTG GTG CTG TCC CAG      3606
Gln Ala Ile Ala Ala Arg Leu Pro Asn Val Asp Leu Val Leu Ser Gln
                940                 945                 950
ACC AAG CAG GAC ATT GCG CGT GCC CGC CGG TTG CAG GCT GAG GCT GAG      3654

GAA GCC AGG AGC CGA GCC CAT GCA GTG GAG GGC CAG GTG GAA GAT GTG      3702
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Glu Ala Arg Ser Arg Ala His Ala Val Glu Gly Gln Val Glu Asp Val
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GTT GGG AAC CTG CGG CAG GGG ACA GTG GCA CTG CAG GAA GCT CAG GAC 3750
Val Gly Asn Leu Arg Gln Gly Thr Val Ala Leu Gln Glu Ala Gln Asp
985 990 995

ACC ATG CAA GGC ACC AGC CGC TCC CTT CGG CTT ATC CAG GAC AGG GTT 3798
Thr Met Gln Gly Thr Ser Arg Ser Leu Arg Leu Ile Gln Asp Arg Val
1000 1005 1010 1015

GCT GAG GTT CAG CAG GTA CTG CGG CCA GCA GAA AAG CTG GTG ACA AGC 3846
Ala Glu Val Gln Gln Val Leu Arg Pro Ala Glu Lys Leu Val Thr Ser
1020 1025 1030

ATG ACC AAG CAG CTG GGT GAC TTC TGG ACA CGG ATG GAG GAG CTC CGC 3894
Met Thr Lys Gln Leu Gly Asp Phe Trp Thr Arg Met Glu Glu Leu Arg
1035 1040 1045

CAC CAA GCC CGG CAG CAG GGG GCA GAG GCA GTC CAG GCC CAG CAG CTT 3942
His Gln Ala Arg Gln Gln Gly Ala Glu Ala Val Gln Ala Gln Gln Leu
1050 1055 1060

GCG GAA GGT GCC AGC GAG CAG GCA TTG AGT GCC CAA GAG GGA TTT GAG 3990
Ala Glu Gly Ala Ser Glu Gln Ala Leu Ser Ala Gln Glu Gly Phe Glu
1065 1070 1075

AGA ATA AAA CAA AAG TAT GCT GAG TTG AAG GAC CGG TTG GGT CAG AGT 4038
Arg Ile Lys Gln Lys Tyr Ala Glu Leu Lys Asp Arg Leu Gly Gln Ser
1080 1085 1090 1095

TCC ATG CTG GGT GAG CAG GGT GCC CGG ATC CAG AGT GTG AAG ACA GAG 4086
Ser Met Leu Gly Glu Gln Gly Ala Arg Ile Gln Ser Val Lys Thr Glu
1100 1105 1110

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1130 1135 1140

TCA GCG GAC CTG ACA GGA CTG GAG AAG CGT GTG GAG CAG ATC CGT GAC 4230

Ser Ala Asp Leu Thr Gly Leu Glu Lys Arg Val Glu Gln Ile Arg Asp

1145 1150 1155

CAC ATC AAT GGG CGC GTG CTC TAC TAT GCC ACC TGC AAG T 4270

His Ile Asn Gly Arg Val Leu Tyr Tyr Ala Thr Cys Lys

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TAAAAATCTT TGGAAAAGAG CCTGGAGGTT CAACGAG 4667

Sequence No.: 26

Sequence length: 1086

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 138.. 506

Characterization method: E

Sequence description

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CTCTAGCCGT CGAGGAGCTG CCTGGGGACG TTTGCCCTGG GGCCCCAGCC TGGCCCGGGT     120

CACCCTGGCA TGAGGAG ATG GGC CTG TTG CTC CTG GTC CCA TTG CTC CTG         170
                      Met Gly Leu Leu Leu Leu Val Pro Leu Leu Leu
                        1               5                  10

CTG CCC GGC TCC TAC GGA CTG CCC TTC TAC AAC GGC TTC TAC TAC TCC        218
Leu Pro Gly Ser Tyr Gly Leu Pro Phe Tyr Asn Gly Phe Tyr Tyr Ser
                15                  20                  25

AAC AGC GCC AAC GAC CAG AAC CTA GGC AAC GGT CAT GGC AAA GAC CTC        266
Asn Ser Ala Asn Asp Gln Asn Leu Gly Asn Gly His Gly Lys Asp Leu
            30                  35                  40

CTT AAT GGA GTG AAG CTG GTG GTG GAG ACA CCC GAG GAG ACC CTG TTC        314
Leu Asn Gly Val Lys Leu Val Val Glu Thr Pro Glu Glu Thr Leu Phe
        45                  50                  55

ACC CGC ATC CTA ACT GTG GGC CCC CAG AGC CTG GGG TCC GAA GCT TTG        362
Thr Arg Ile Leu Thr Val Gly Pro Gln Ser Leu Gly Ser Glu Ala Leu
    60                  65                  70                  75

GCT TCC CCG ACC CGC AGA GCC GCT TGT ACG GTG TTT ACT GCT ACC GCC        410
Ala Ser Pro Thr Arg Arg Ala Ala Cys Thr Val Phe Thr Ala Thr Ala
                80                  85                  90

AGC ACT AGG ACC TGG GGC CCT CCC CTG CCG CAT TCC CTC ACT GGC TGT        458
Ser Thr Arg Thr Trp Gly Pro Pro Leu Pro His Ser Leu Thr Gly Cys
            95                  100                 105

            110                 115                 120
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TAACTGT TTTTATACTT CTCAATTTAA ATTTTCTTTA AACATTTTTT TACTATTTTT 560

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TGCTTGCTCC CCTGGGCCAT TTGCGGTTTT GTGGGCTTCT GGAGGGTTCC CCGCCATCCA 680

GGCTGGTCTC CCTCCCTTAA GGAGGTTGGT GCCCAGAGTG GGCGGTGGCC TGTCTAGAAT 740

GCCGCCGGGA GTCCGGGCAT GGTGGGCACA GTTCTCCCTG CCCCTCAGCC TGGGGGAAGA 800

AGAGGGCCTC GGGGGCCTCC GGAGCTGGGC TTTGGGCCTC TCCTGCCCAC CTCTACTTCT 860

CTGTGAAGCC GCTGACCCCA GTCTGCCCAC TGAGGGGCTA GGGCTGGAAG CCAGTTCTAG 920

GCTTCCAGGC GAAAGCTGAG GGAAGGAAGA AACTCCCCTC CCCGTTCCCC TTCCCCTCTC 980

GGTTCCAAAG AATCTGTTTT GTTGTCATTT GTTTCTCCTG TTTCCCTGTG TGGGGAGGGG 1040

CCCTCAGGTG TGTGTACTTT GGACAATAAA TGGTGCTATG ACTGCC 1086

Sequence No.: 27

Sequence length: 866

Sequence type: Nucleic acid

Strandedness: Double

Topology: Linear

Sequence kind: cDNA to mRNA

Original source:

Organism species: *Homo sapiens*

Cell kind: Stomach cancer

Clone name: HP10368

Sequence characteristics:

Code representing characteristics: CDS

Existence site: 73.. 600

Characterization method: E

Sequence description

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Ala Leu Ser Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala
     15                  20                  25
AAA AAG GAC ACA AAG GAC TCT CGA CCC AAA CTG CCC CAG ACC CTC TCC      207
Lys Lys Asp Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser
 30                  35                  40                  45
AGA GGT TGG GGT GAC CAA CTC ATC TGG ACT CAG ACA TAT GAA GAA GCT      255
Arg Gly Trp Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala
                 50                  55                  60
CTA TAT AAA TCC AAG ACA AGC AAC AAA CCC TTG ATG ATT ATT CAT CAC      303
Leu Tyr Lys Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His
             65                  70                  75
TTG GAT GAG TGC CCA CAC AGT CAA GCT TTA AAG AAA GTG TTT GCT GAA      351
Leu Asp Glu Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu
         80                  85                  90
AAT AAA GAA ATC CAG AAA TTG GCA GAG CAG TTT GTC CTC CTC AAT CTG      399
Asn Lys Glu Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu
     95                  100                 105
GTT TAT GAA ACA ACT GAC AAA CAC CTT TCT CCT GAT GGC CAG TAT GTC      447
Val Tyr Glu Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val
110                 115                 120                 125
CCC AGG ATT ATG TTT GTT GAC CCA TCT CTG ACA GTT AGA GCC GAT ATC      495
Pro Arg Ile Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile
                130                 135                 140
ACT GGA AGA TAT TCA AAC CGT CTC TAT GCT TAC GAA CCT GCA GAT ACA      543

GCT CTG TTG CTT GAC AAC ATG AAG AAA GCT CTC AAG TTG CTG AAG ACT      591
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Ala Leu Leu Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr

160 165 170

GAA TTG TAAAGAAAAA AAATCTCCAA GCCCTTCTGT CTGTCAGGCC TTG 640

Glu Leu

175

AGACTTGAAA CCAGAAGAAG TGTGAGAAGA CTGGCTAGTG TGGAAGCATA GTGAACACAC 700

TGATTAGGTT ATGGTTTAAT GTTACAACAA CTATTTTTTA AGAAAAACAA GTTTTAGAAA 760

TTTGGTTTCA AGTGTACATG TGTGAAAACA ATATTGTATA CTACCATAGT GAGCCATGAT 820

TTTCTAAAAA AAAAAATAAA TGTTTTGGGG GTGTTCTGTT TTCTCC 866

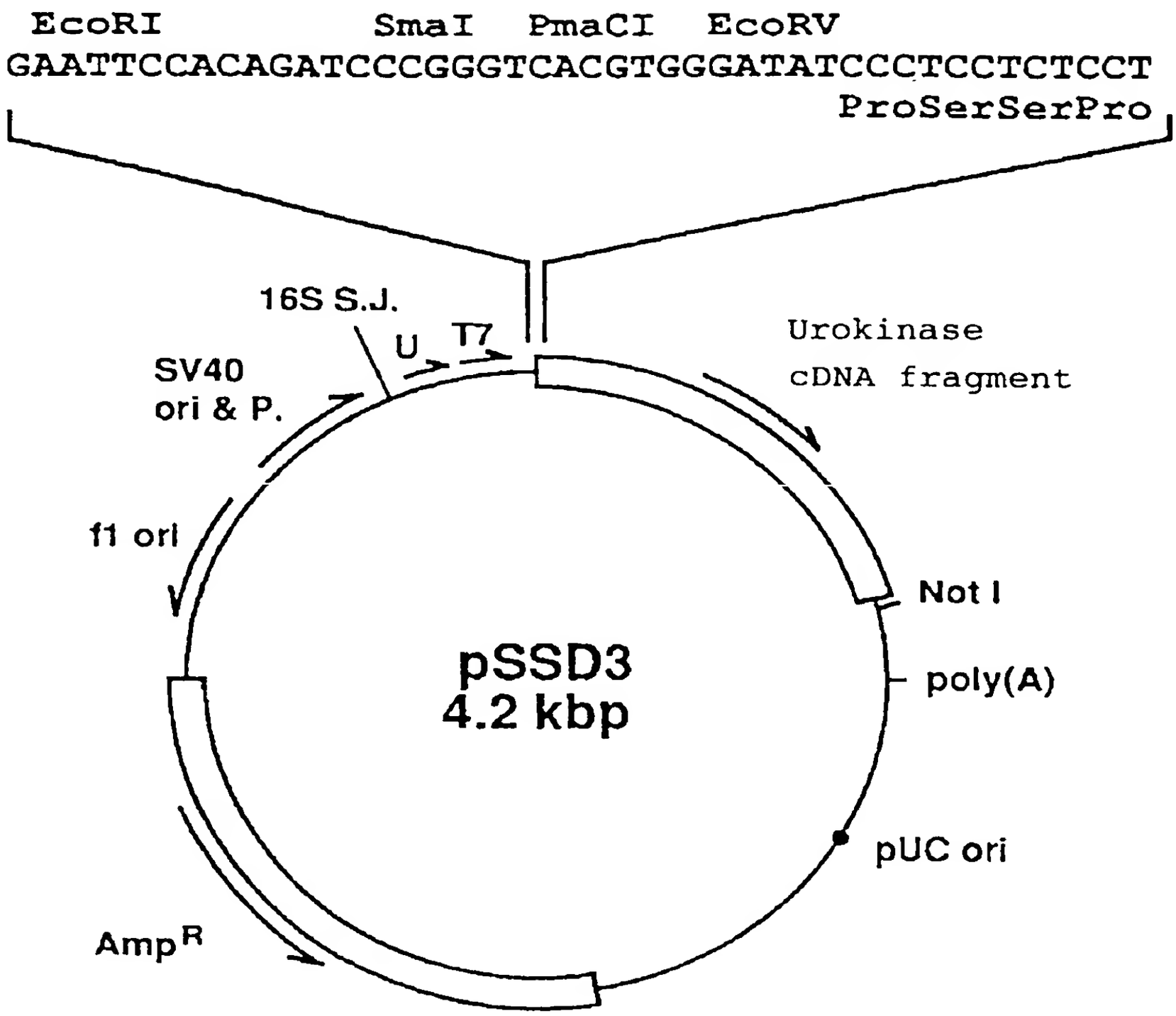
Claims

1. Proteins containing any of the amino acid sequences represented by Sequence No. 1 to Sequence No. 9.

2. DNAs encoding any of the proteins as described in Claim 1.

3. cDNAs containing any of the base sequences represented by Sequence No. 10 to Sequence No. 18.

4. cDNAs described in Claim 3 which comprise any of the base sequences represented by Sequence No. 19 to Sequence No. 27.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ProSerSerPro
16S S.J.
U
T7
SV40
ori & P.
Urokinase
cDNA fragment
f1 ori
Not I
poly(A)
pSSD3
4.2 kbp
pUC ori
Amp^R

Fig.1

Fig. 2

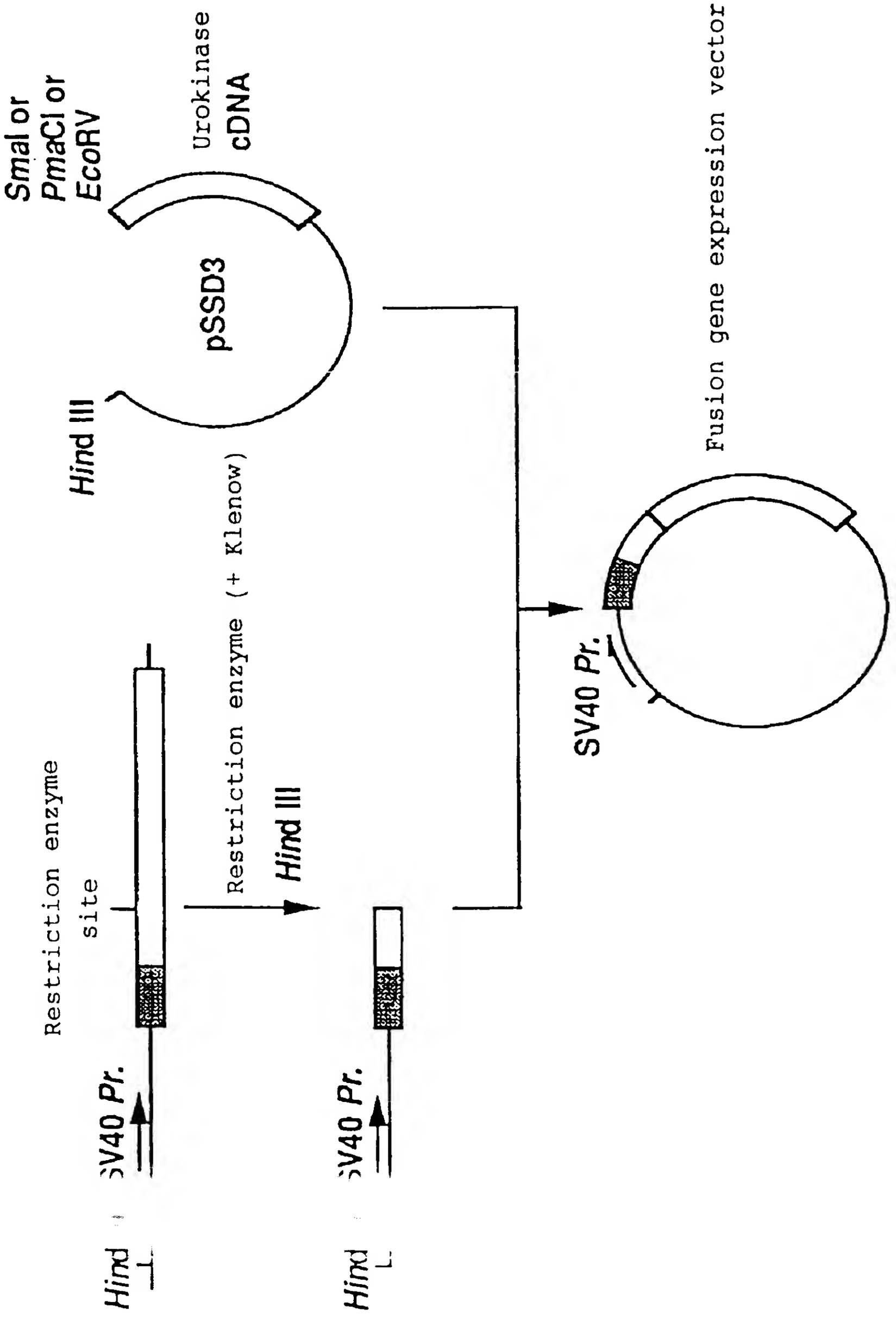
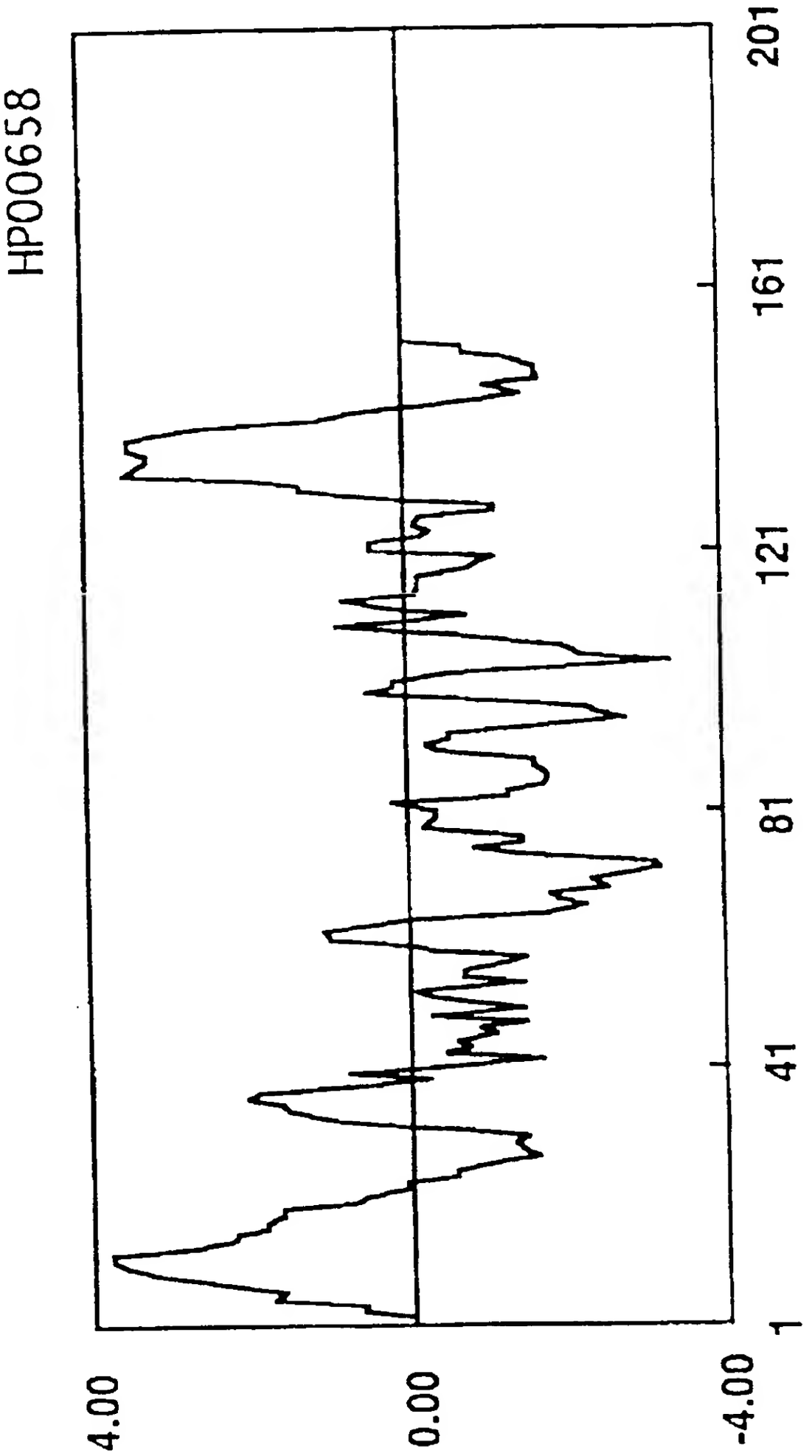

Restriction enzyme site
Hind III
SV40 Pr.
Restriction enzyme (+ Klenow)
Hind III
pSSD3
Urokinase cDNA
SmaI or PmaCI or EcoRV
Hind III
SV40 Pr.
Fusion gene expression vector

Fig.3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-4.00
Hydrophobicity/Hydrophilicity
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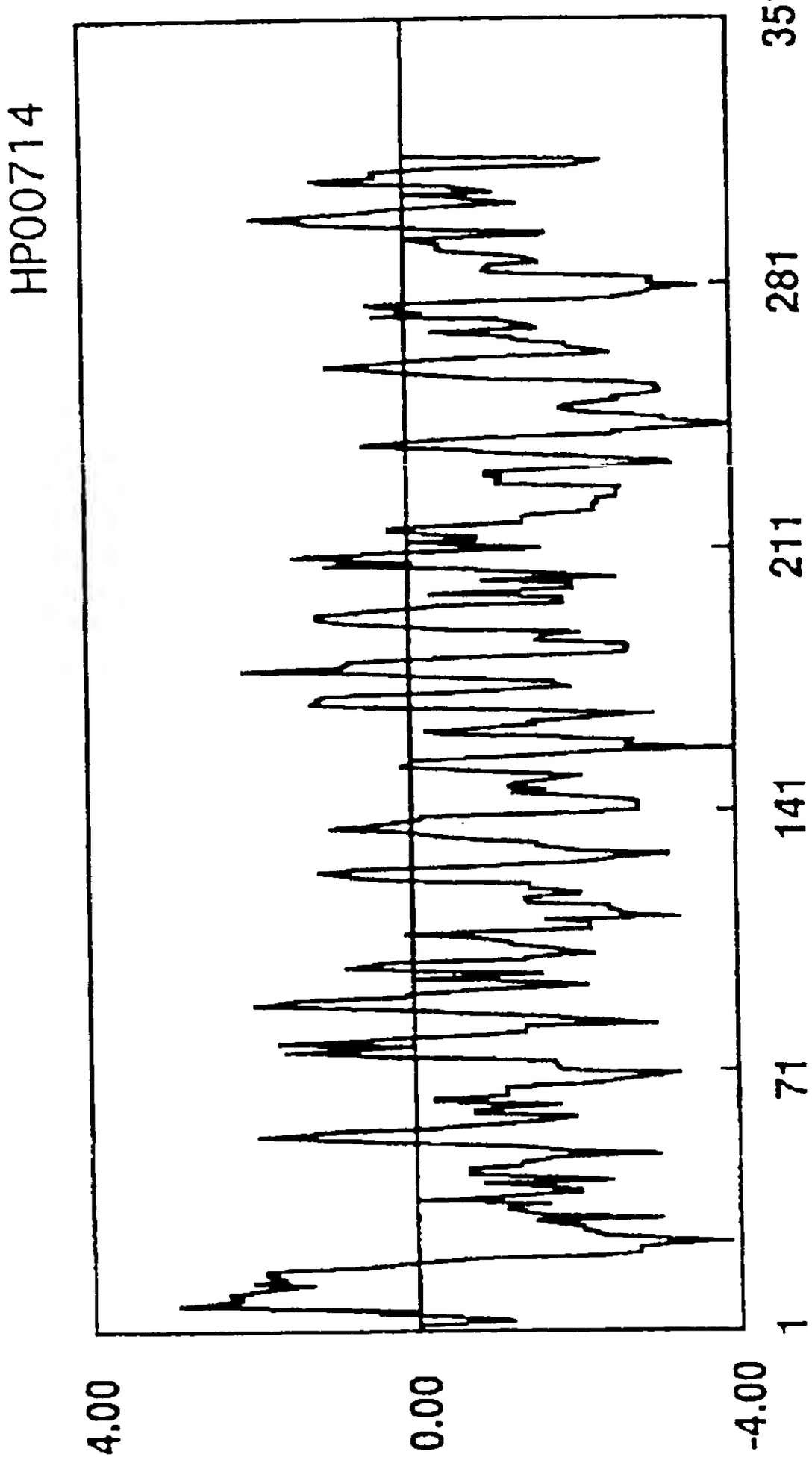
81
121
161
201
Amino acid Residue Number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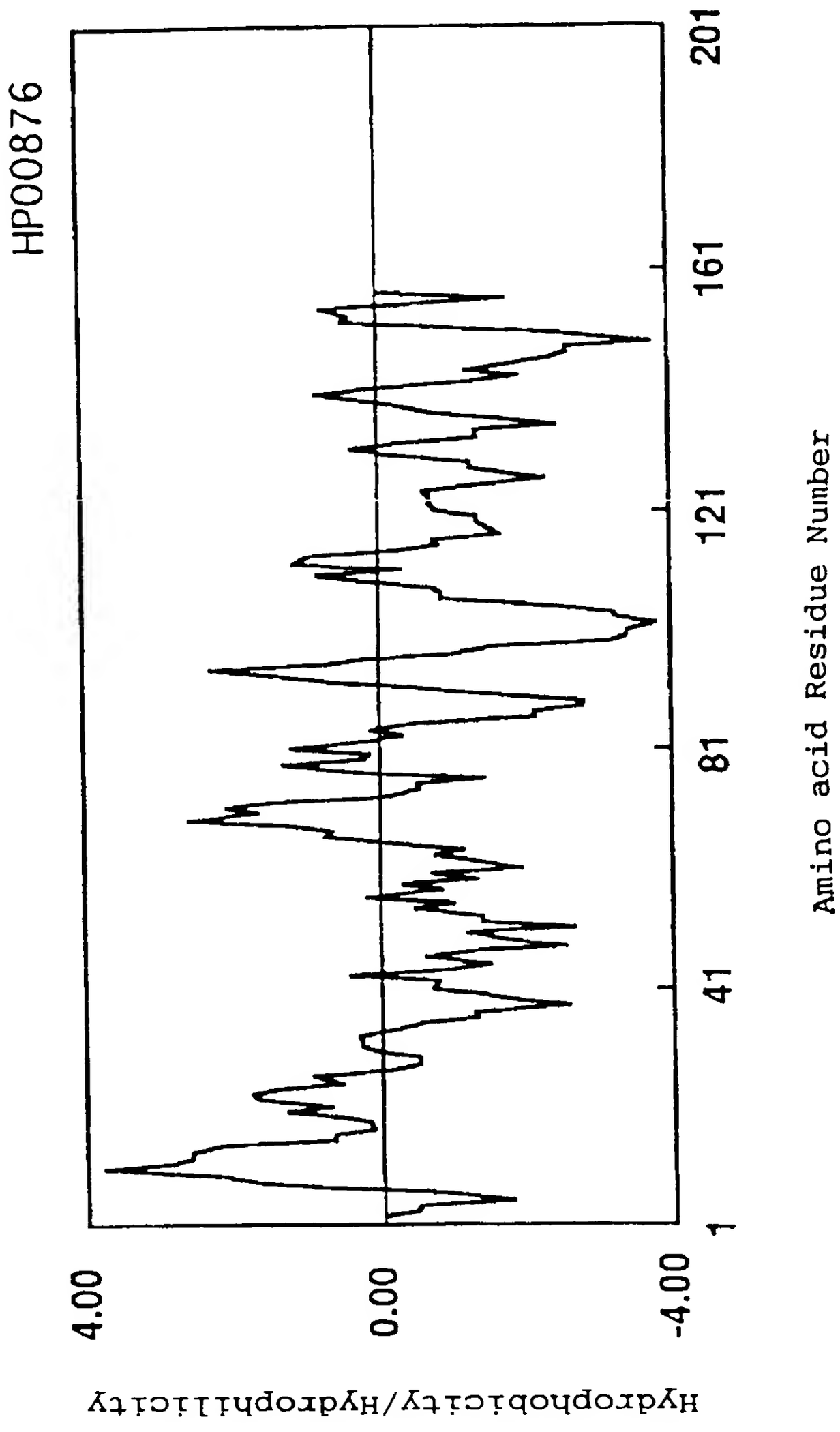
Hydrophobicity/Hydrophilicity

Fig.4

Fig.5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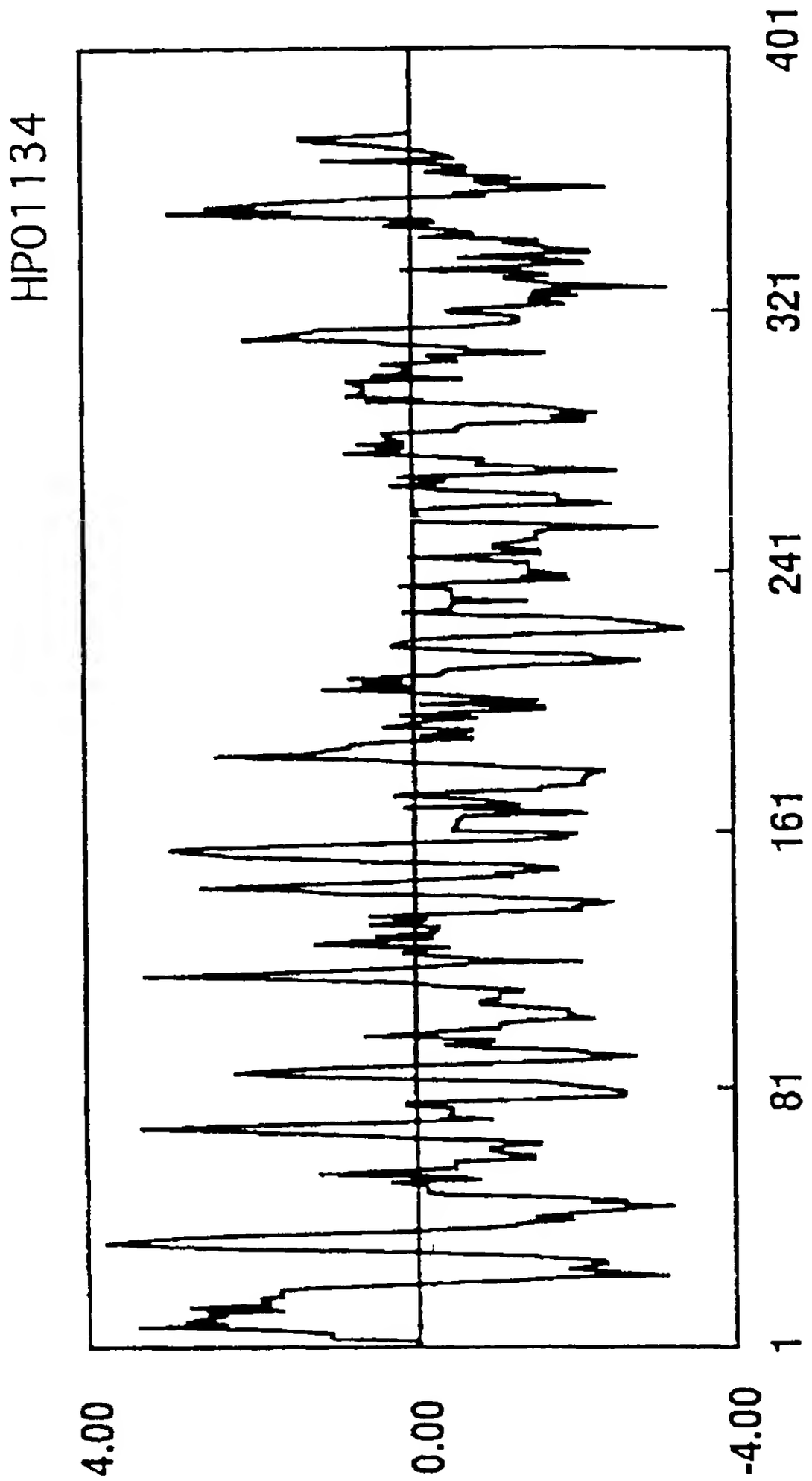
201
Amino acid Residue Number

Fig.6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81
1
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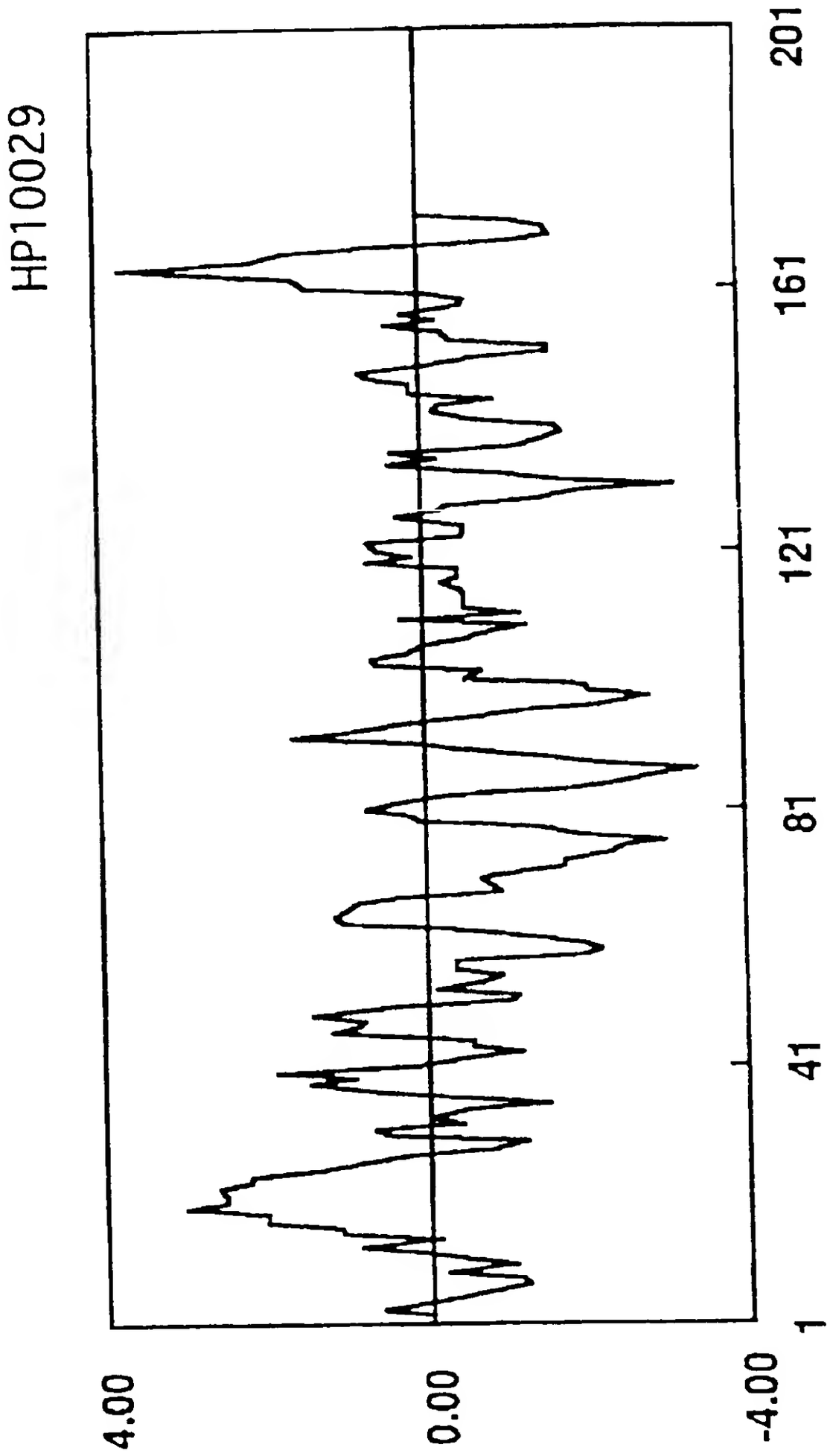
Hydrophobicity/Hydrophilicit

Fig.7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201
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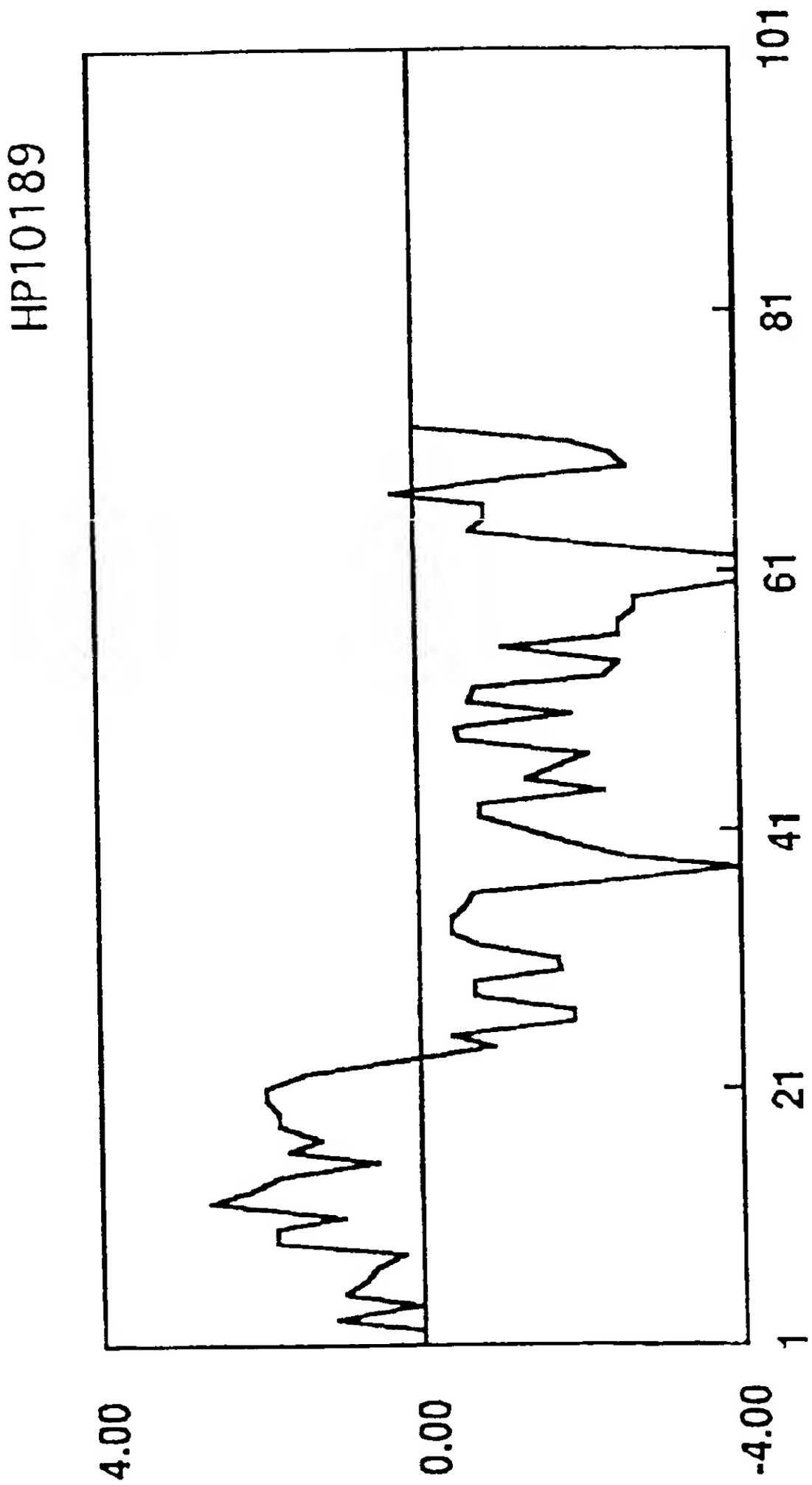
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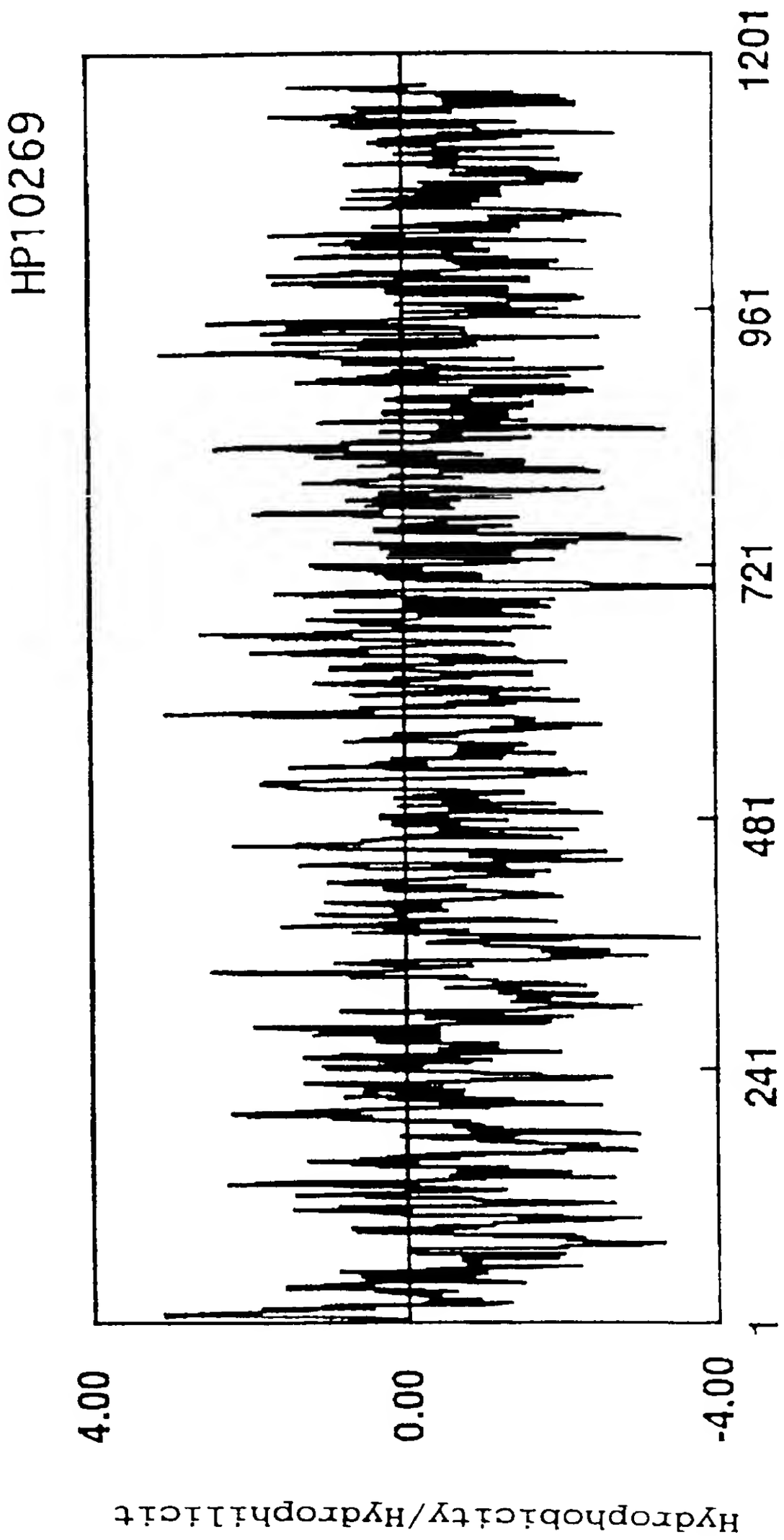
41
21
1
4.00
0.00
-4.00
Hydrophobicity/Hydrophilicity
Amino acid Residue Number

Fig.8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721
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241
1
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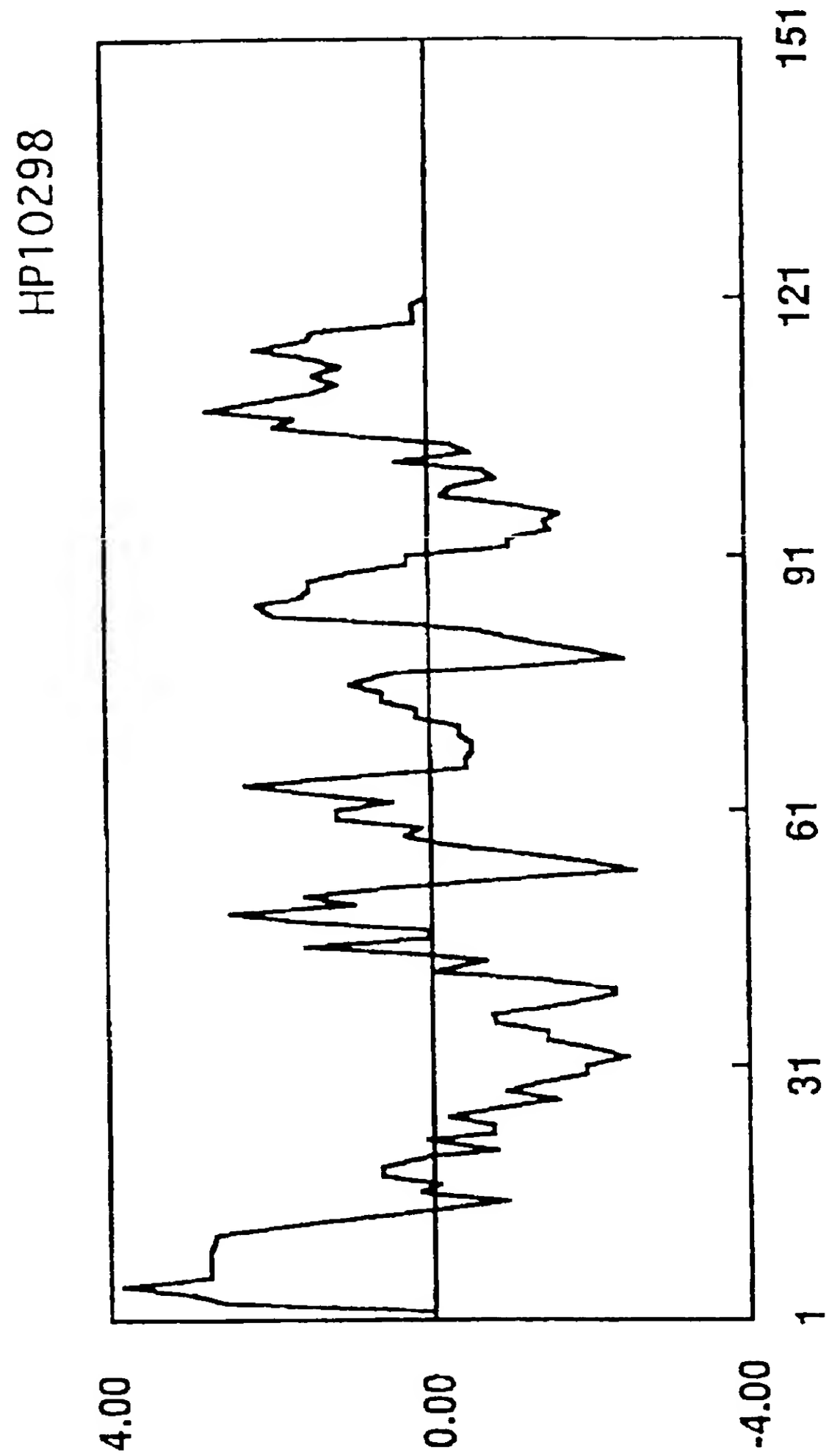
0.00
-4.00
Hydrophobicity/Hydrophilicit
Amino acid Residue Numbe

Fig.9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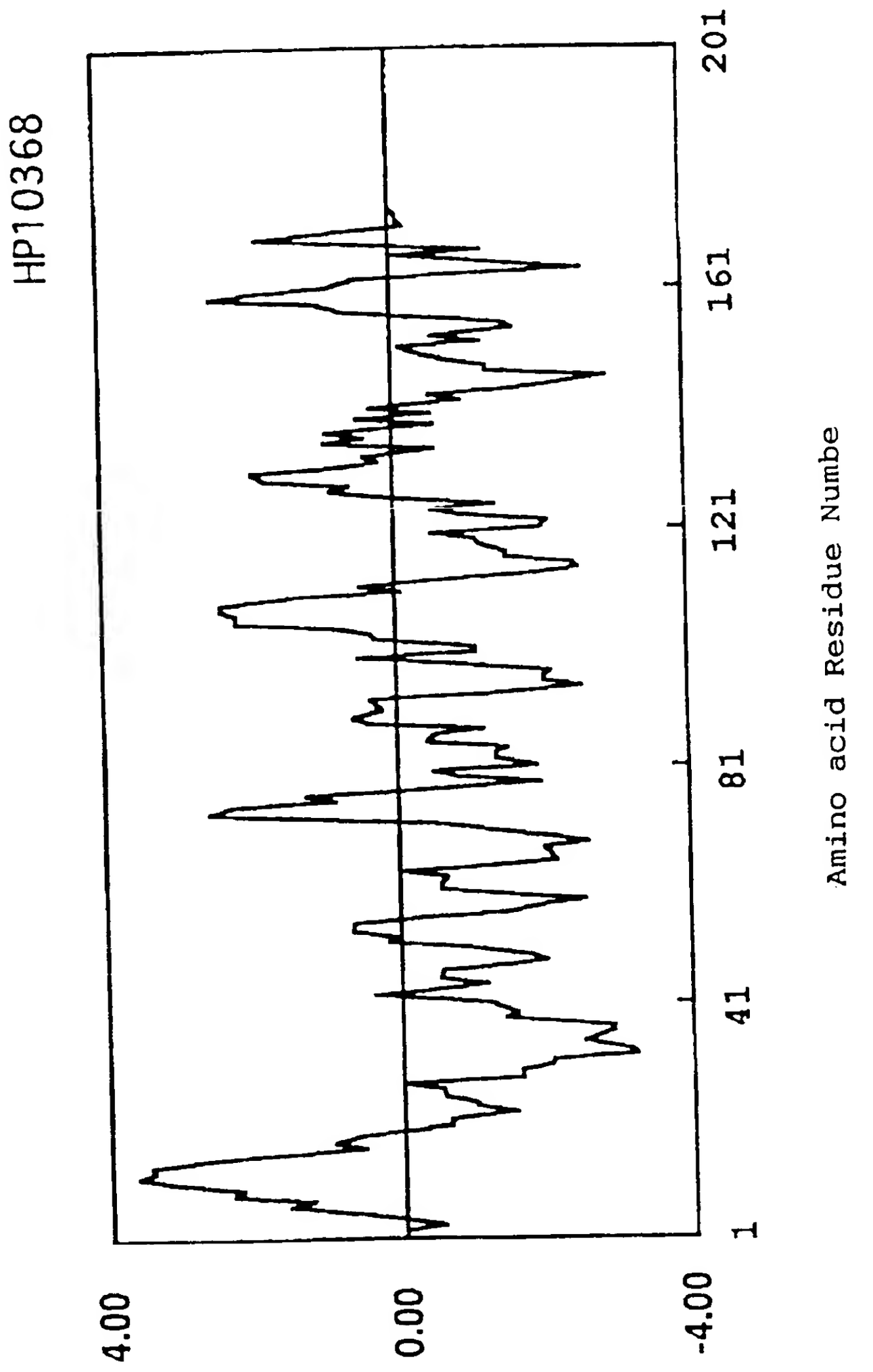
Hydrophobicity/Hydrophilicit

Fig.10

fig.11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Hydrophobicity/Hydrophilicit
Amino acid Residue Numbe